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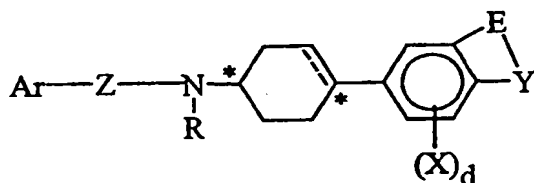
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(54) Title: BICICLIC CYCLOHEXYLAMINES AND THEIR USE AS NMDA RECEPTOR ANTOGONISTS



(I)

(57) Abstract: Described are bicycle-substituted cyclohexylamines of Formula (I) and their pharmaceutically acceptable salts thereof. The compounds are antagonists of NMDA receptor channel complexes useful for treating cerebral vascular disorders such as, for example, cerebral ischemia, cardiac arrest, stroke, and Parkinson's disease. The substituents are defined in the

specification.

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## BICYCLIC CYCLOHEXYLAMINES AND THEIR USE AS NMDA RECEPTOR ANTAGONISTS

## FIELD OF THE INVENTION

The invention pertains to bicycle-substituted cyclohexylamine derivatives  
5 as N-Methyl-D-Aspartate Antagonists (NMDA).

## BACKGROUND OF THE INVENTION

Over excitation of NMDA receptor channel complexes on postsynaptic  
neurons following excessive release of glutamic acid from synaptosomes and  
glutamic acid from synaptosomes and glial cells results in excessive calcium ion  
10 influx into the neuronal cells, which leads to their death. This is believed to occur  
under ischemic or hypoxic conditions such as stroke, hypoglycemic, cardiac arrest  
and physical trauma. An NMDA receptor antagonist might be therapeutically useful  
because it may minimize damage of the central nervous system induced by ischemic  
or hypoxic conditions. The NMDA receptor channel complex consists of at least  
15 three binding domains including a glutamic acid (or NMDA) recognition site, a  
channel blocking binding site, and a strychnine-insensitive glycine binding type.  
Physiologically, a blockade of at least one of these sites terminates the channel  
opening of the NMDA receptor to prevent a calcium ion influx. (Nagata R., et al., *J.*  
*Med. Chem.*, 1994;37:3956-3968)

20 Excessive excitation of NMDA receptor channel complexes by  
neurotransmitters may be responsible for the loss of neurons in cerebral vascular  
disorders such as cerebral ischemia or cerebral infarction resulting in a range of  
conditions such as thromboembolic or hemorrhagic stroke, cerebral vasospasm,  
hypoglycemia, cardiac arrest, status epilepticus, perinatal asphyxia, anoxia, such  
25 as from near drowning, pulmonary surgery and cerebral trauma, as well as  
lathyrism, Alzheimer's disease, and Huntington's disease. Such conditions  
likewise suggest the use of agents that may act as antagonists in the receptors  
identified above may lead to treatment of amyotrophic lateral sclerosis (ALS),

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schizophrenia, Parkinsonism, epilepsy, anxiety, pain, and drug addiction.  
(PCT/EPO 94/01492 having publication number WO 94/26747 published  
November 24, 1994, Watjen et al.)

5 L-glutamic acid, L-aspartic acid, and a number of other closely related  
amino acids have the ability to activate neurons in the nervous system, and  
therefore the vast majority of excitatory neurons in the mammalian CNS.  
Interaction with glutamic acid mediated neurotransmission is considered a useful  
approach in the treatment of neurological and psychiatric diseases.  
(WO 94/26746, published November 24, 1994, Jacobsen et al.)

10 Excitatory amino acid receptor antagonists that block NMDA receptors are  
recognized for usefulness in the treatment of a variety of disorders. NMDA  
receptors are intimately involved in the phenomenon of excitotoxicity, which  
may be a critical determinant of outcome of several neurological disorders.  
Disorders known to be responsive to blockade of the NMDA receptor include  
15 acute cerebral ischemia (stroke or cerebral trauma, for example), muscular spasm,  
convulsive disorders, neuropathic pain, and anxiety, and may be a significant  
causal factor in chronic neurodegenerative disorders such as Parkinson's disease  
(Klockgether T., Turski L., *Ann. Neurol.*, 1993;34:585-59), human  
immunodeficiency virus (HIV) related neuronal injury, amyotrophic lateral  
20 sclerosis (ALS), Alzheimer's disease (Francis P.T., Sims N.R., Procter A.W.,  
Bowen D.M., *J. Neurochem.*, 1993;60(5):1589-1604), and Huntington's disease  
(see Lipton S., *TINS*, 1993;16(12):527-532; Lipton S.A., Rosenberg P.A., *New  
Eng. J. Med.*, 1994;330(9):613-622; and Bigge C.F., *Biochem. Pharmacol.*,  
1993;45:1547-1561 and references cited therein). NMDA receptor antagonists  
25 may also be used to prevent tolerance to opiate analgesia or to help control  
withdrawal symptoms from addictive drugs (European Patent Application  
488,959A).

Many of the properties of native NMDA receptors are seen in recombinant  
homomeric NR1 receptors. These properties are altered by the NR2 subunits.  
30 Recombinant NMDA receptors expressed in *Xenopus* Oocytes have been studied  
by voltage-clamp recording, and have been found to exhibit developmental and  
regional expression of the mRNAs encoding NMDA receptor subunits.  
Electrophysiological assays were utilized to characterize the actions of

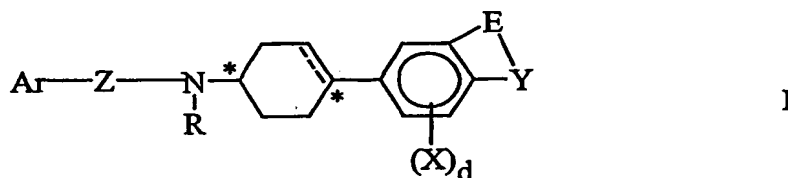
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compounds at NMDA receptors expressed in *Xenopus* Oocytes. The compounds were assayed at four subunit combinations at cloned rat NMDA receptors, corresponding to three putative NMDA receptor subtypes (Moriyoshi et al., *Nature*, 1991;354:31-37; Monyer et al., *Science*, 1992;256:1217-1221; Kutsuwada et al., *Nature*, 1992:358;36-41; Sugihara et al., *Biochem. Biophys Res. Commun.*, 1992;185:826-832).

Expression cloning of the first NMDA receptor subunit, NMDAR1 (NR1) in Nakanishi's lab in 1991 provided an initial view of the molecular structure of the NMDA receptor (Moriyoshi et al., supra, 1991). There are several other structurally related subunits (NMDAR2A through NMDAR2D) that join NR1 in heteromeric assemblies to form the functional ion channel complex of the receptor (*Annu. Rev. Neurosci.*, 1994;17:31-108). The molecular heterogeneity of NMDA receptors implies a future potential for agents with subtype selective pharmacology.

## SUMMARY OF THE INVENTION

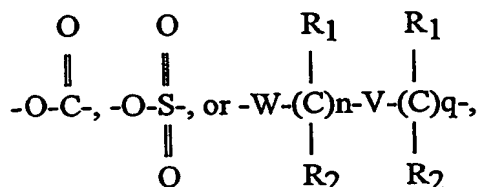
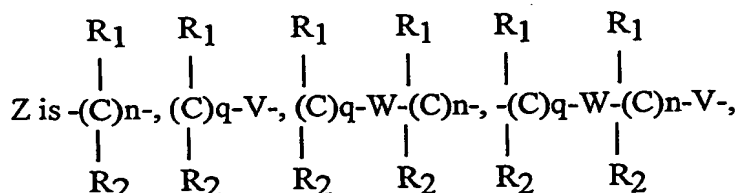
Described are bicycle-substituted cyclohexyl amines of Formula I and their pharmaceutically acceptable salts thereof



wherein:

Ar is substituted 1 to 3 times or unsubstituted aryl or substituted 1 to 3 times or unsubstituted heteroaryl, which heteroaryl is from 5 to 14 atoms having from 1 to 2 heteroatoms selected from N, O, and S wherein the substituents are selected from the groups F, Cl, Br, I, OH, NH<sub>2</sub>, SH, CN, NO<sub>2</sub>, OCH<sub>3</sub>, OC(O)CH<sub>3</sub>, CF<sub>3</sub>, OCH<sub>2</sub>CH<sub>2</sub>OH, NHC(O)CH<sub>3</sub>, NHCH<sub>3</sub>, or N(CH<sub>3</sub>)<sub>2</sub>;

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wherein V is  $\begin{array}{c} \text{O} \\ | \\ \text{-(CH}_2\text{)}_n\text{-} \end{array}$ ,  $\text{-C-}$ ,  $\text{-S(O)-}$ , or  $\text{-S(O)}_2\text{-}$ ,

W is  $\begin{array}{c} \text{O} \\ || \\ \text{-(CH}_2\text{)}_n\text{-} \end{array}$ ,  $\text{-C-}$ ,  $\text{-S(O)-}$ ,  $\text{-S(O)}_2\text{-}$ ,  $\text{-O-}$ ,  $\text{-S-}$ ,  $\text{-C}\equiv\text{C-}$ , or *entgegen* or *zusammen* -  
 $\text{CH(R}_1\text{)=CH(R}_2\text{)-}$ ,

d is an integer from 0 to 2;

n is an integer from 1 to 6;

q is an integer from 0 to 6;

R<sub>1</sub> and R<sub>2</sub> are independently selected from the group consisting of hydrogen,

alkyl, OH, hydroxyalkyl, aminoalkyl, aralkyl, or N(R<sub>4</sub>)(R<sub>5</sub>) wherein

R<sub>4</sub> and R<sub>5</sub> are independently selected from hydrogen, alkyl, aralkyl,

heteroaryl, heteroaralkyl, aminoalkyl, hydroxyalkyl, and thioalkyl;

R is hydrogen, alkyl, C(O)R<sub>6</sub>, C(O)OR<sub>6</sub>, C(O)NHR<sub>6</sub>, -alkyl-C(O)NH<sub>2</sub>, aralkyl,

(C<sub>3</sub>-C<sub>7</sub> cycloalkyl)-alkyl, hydroxyalkyl, aminoalkyl,

amino(hydroxy)alkyl, carboxyalkyl, heteroaralkyl, alkenylalkyl, or OH

wherein R<sub>6</sub> is alkyl or aralkyl;

X is independently selected from hydrogen or an electron withdrawing group; and

E-Y- is

$\text{-CH=CH-N(H)-}$ ,

$\text{-(CH}_2\text{)}_2\text{-N(H)-}$ ,

$\text{-CH=N-N(H)-}$ ,

$\text{-C(O)-CH}_2\text{-N(H)-}$ ,

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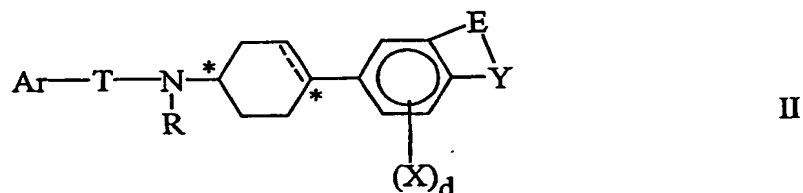
5  
-CH<sub>2</sub>-C(O)-N(H)-,  
-CH<sub>2</sub>-S(O)-N(H)-,  
-CH<sub>2</sub>-S(O)<sub>2</sub>-N(H)-,  
-CH=CH-CH(OH)-,  
-(CH<sub>2</sub>)<sub>2</sub>-CH(OH)-,  
-C(O)-CH<sub>2</sub>-C(O)-,  
-C(O)-NH-C(O)-,  
-N=CH-N(H)-,  
-N(H)-C(O)-N(H)-,  
10  
-O-C(O)-NH-,  
-S-C(O)-NH-,  
-O-N=CH(OH)-,  
-S-N=CH(OH)-,  
-N=N-N(H)-,  
15  
-CH=CH-CH=C(OH)-,  
-(CH<sub>2</sub>)<sub>3</sub>-CH(OH)-,  
-(CH<sub>2</sub>)<sub>2</sub>-S(O)-N(H)-,  
-(CH<sub>2</sub>)<sub>2</sub>-S(O)<sub>2</sub>-N(H)-,  
-CH=CH-C(O)-N(H)-,  
20  
-C(O)-NH-N=C(OH)-,  
-CH=N-NH-C(O)-,  
-CH=N(O)-N=C(OH)-,  
-N(H)-C(O)-N(H)-C(O)-,  
-N=CH-C(O)-NH-,  
25  
-O-CH<sub>2</sub>-C(O)-NH-,  
-S-CH<sub>2</sub>-C(O)-NH-, or  
-N(H)-C(O)-C(O)-N(H)-;

-- denotes a single or double bond; and

\* denotes *cis* or *trans* or a mixture thereof.

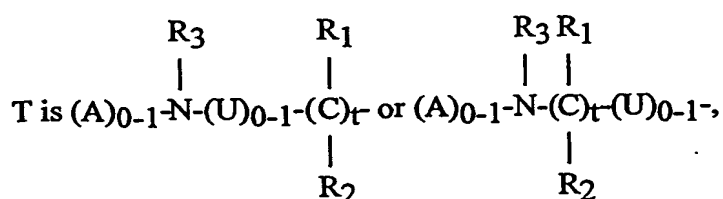
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The invention also relates to compounds of Formula II



or a pharmaceutically acceptable salt thereof  
wherein:

Ar, R, X, d, and -E-Y- are as defined above;



wherein U is  $-\text{CH}_2-$ ,  $-\overset{\overset{\text{O}}{\parallel}}{\text{C}}-$ ,  $-\text{S}(\text{O})-$ , or  $-\text{S}(\text{O})_2-$ ,

A is  $-\text{CH}_2-$ ,  $-\overset{\overset{\text{O}}{\parallel}}{\text{C}}-$ ,  $-\text{S}(\text{O})-$ , or  $-\text{S}(\text{O})_2-$ ,

t is an integer from 1 to 3,

R<sub>1</sub> and R<sub>2</sub> are independently selected from hydrogen, alkyl, OH, hydroxyalkyl, aminoalkyl, thioalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, guanidiny, (aminocarbonyl)alkyl-, carboxyalkyl-, (methylthio)-alkyl-, or N(R<sub>4</sub>)(R<sub>5</sub>), wherein R<sub>4</sub> and R<sub>5</sub> are independently selected from hydrogen, alkyl, aralkyl, heteroaryl, heteroaralkyl, ureidoalkyl, aminoalkyl, hydroxyalkyl, or thioalkyl;

R<sub>3</sub> is hydrogen, alkyl, OH, or aralkyl;

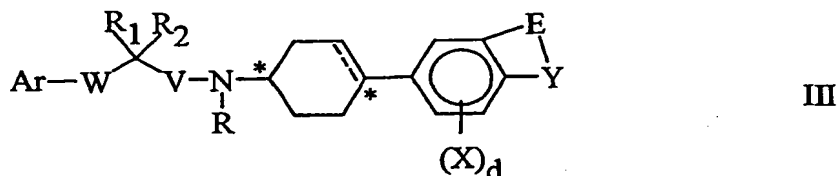
R is hydrogen, alkyl, C(O)R<sub>6</sub>, C(O)OR<sub>6</sub>, C(O)NHR<sub>6</sub>, alkyl -CO<sub>2</sub>NH<sub>2</sub>, aralkyl, hydroxyalkyl, (C<sub>3</sub>-C<sub>7</sub> cycloalkyl) alkyl, aminoalkyl, amino(hydroxy)alkyl, carboxyalkyl, heteroaralkyl, alkenyl-alkyl, or OH wherein R<sub>6</sub> is alkyl or aralkyl;

X is independently selected from hydrogen or an electron withdrawing group; and

\* denotes *cis* or *trans* or a mixture thereof.

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The invention also relates to compounds of Formula III:



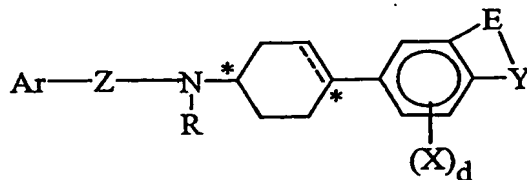
wherein the substituents are defined above.

The invention is also concerned with a pharmaceutical composition useful for treating disorders responsive to the selective blockade of N-methyl-D-aspartate receptor subtypes utilizing the compounds of Formula I or Formula II or Formula III and the pharmaceutically acceptable salts thereof, optionally disorders as stroke, cerebral ischemia, trauma, hypoglycemia, neurodegenerative disorders, anxiety, depression, migraine headache, convulsions, aminoglycoside antibiotics-induced hearing loss, psychosis, glaucoma, CMV retinitis, opioid tolerance or withdrawal, chronic pain, or urinary incontinence.

The invention is also concerned with a method of treating disorders responsive to the selective blockade of the N-methyl-D-aspartate receptor subtypes in a mammal suffering thereof which comprises administering in unit dosage form, at least one compound represented by Formula I or Formula II or Formula III above or its pharmaceutically acceptable salts thereof.

### DETAILED DESCRIPTION OF THE INVENTION

The invention is concerned with bicycle-substituted cyclohexylamines of Formula I and their pharmaceutically acceptable salts thereof:



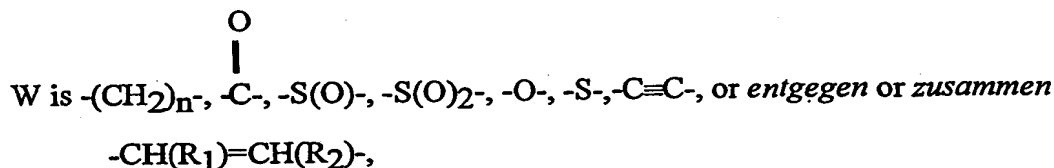
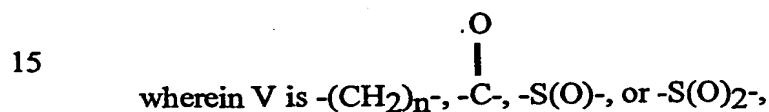
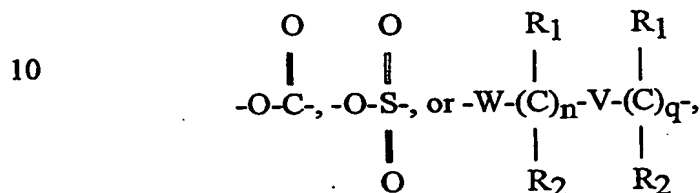
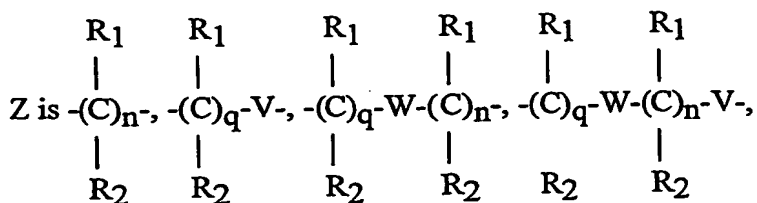
wherein:

Ar is substituted 1 to 3 times or unsubstituted aryl or substituted 1 to 3 times or unsubstituted heteroaryl, which heteroaryl is from 5 to 14 atoms having from 1 to 2 heteroatoms selected from N, O, and S wherein the



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substituents are selected from the groups F, Cl, Br, I, OH, NH<sub>2</sub>, SH, CN, NO<sub>2</sub>, OCH<sub>3</sub>, OC(O)CH<sub>3</sub>, CF<sub>3</sub>, OCH<sub>2</sub>CH<sub>2</sub>OH, NHC(O)CH<sub>3</sub>, NHCH<sub>3</sub>, or N(CH<sub>3</sub>)<sub>2</sub>;



d is an integer from 0 to 2;

n is an integer from 1 to 6;

q is an integer from 0 to 6;

R<sub>1</sub> and R<sub>2</sub> are independently selected from the group consisting of hydrogen,

25 alkyl, OH, hydroxyalkyl, aminoalkyl, aralkyl, or N(R<sub>4</sub>)(R<sub>5</sub>) wherein

R<sub>4</sub> and R<sub>5</sub> are independently selected from hydrogen, alkyl, aralkyl,

heteroaryl, heteroaralkyl, aminoalkyl, hydroxyalkyl, and thioalkyl;

R is hydrogen, alkyl, C(O)R<sub>6</sub>, C(O)OR<sub>6</sub>, C(O)NHR<sub>6</sub>, -alkyl-C(O)NH<sub>2</sub>, aralkyl,

(C<sub>3</sub>-C<sub>7</sub> cycloalkyl)-alkyl, hydroxyalkyl, aminoalkyl,

30 amino(hydroxy)alkyl, carboxyalkyl, heteroaralkyl, alkenylalkyl, or OH

wherein R<sub>6</sub> is alkyl or aralkyl;

X is independently selected from hydrogen or an electron withdrawing group; and

-E-Y- is



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- 5       $-(\text{CH}_2)_2\text{-N(H)-}$ ,  
          $-\text{CH=N-N(H)-}$ ,  
          $-\text{C(O)-CH}_2\text{-N(H)-}$ ,  
          $-\text{CH}_2\text{-C(O)-N(H)-}$ ,  
          $-\text{CH}_2\text{-S(O)-N(H)-}$ ,  
          $-\text{CH}_2\text{-S(O)}_2\text{-N(H)-}$ ,  
          $-\text{CH=CH-CH(OH)-}$ ,  
          $-(\text{CH}_2)_2\text{-CH(OH)-}$ ,  
          $-\text{C(O)-CH}_2\text{-C(O)-}$ ,  
10       $-\text{C(O)-NH-C(O)-}$ ,  
          $-\text{N=CH-N(H)-}$ ,  
          $-\text{N(H)-C(O)-N(H)-}$ ,  
          $-\text{O-C(O)-NH-}$ ,  
          $-\text{S-C(O)-NH-}$ ,  
15       $-\text{O-N=CH(OH)-}$ ,  
          $-\text{S-N=CH(OH)-}$ ,  
          $-\text{N=N-N(H)-}$ ,  
          $-\text{CH=CH-CH=C(OH)-}$ ,  
          $-(\text{CH}_2)_3\text{-CH(OH)-}$ ,  
20       $-(\text{CH}_2)_2\text{-S(O)-N(H)-}$ ,  
          $-(\text{CH}_2)_2\text{-S(O)}_2\text{-N(H)-}$ ,  
          $-\text{CH=CH-C(O)-N(H)-}$ ,  
          $-\text{C(O)-NH-N=C(OH)-}$ ,  
          $-\text{CH=N-NH-C(O)-}$ ,  
25       $-\text{CH=N(O)-N=C(OH)-}$ ,  
          $-\text{N(H)-C(O)-N(H)-C(O)-}$ ,  
          $-\text{N=CH-C(O)-NH-}$ ,  
          $-\text{O-CH}_2\text{-C(O)-NH-}$ ,  
          $-\text{S-CH}_2\text{-C(O)-NH-}$ , or  
30       $-\text{N(H)-C(O)-C(O)-N(H)-}$ ; and

\* denotes *cis* or *trans* or a mixture thereof.

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In the compounds of the present invention preferred are compounds of Formula I or pharmaceutically acceptable salts thereof wherein:

X is independently selected from hydrogen or an electron withdrawing group selected from the group consisting of halogen, nitro, cyano, aminoalkyl, CF<sub>3</sub>, C(O)CH<sub>3</sub>, and haloalkyl.

More preferred are compounds of Formula I or pharmaceutically acceptable salts thereof wherein:

Ar is unsubstituted or substituted phenyl;

X is independently selected from hydrogen or an electron withdrawing group selected from the group consisting of halogen, nitro, cyano, aminoalkyl, CF<sub>3</sub>, C(O)CH<sub>3</sub>, and haloalkyl; and

-E-Y- is selected from  $\text{-O-C(=O)-NH-}$ ,  $\text{-S-C(=O)-NH-}$ ,  $\text{-CH=CH-NH-}$ ,  $\text{-N=CH-NH-}$ ;

$\text{-NH-C(=O)-NH-}$ ,  $\text{-N=N-NH-}$ , and  $\text{-NH-C(=O)-C(=O)-NH-}$ ;

\* denotes *trans*.

Still more preferred are compounds of Formula I or pharmaceutically acceptable salts thereof wherein:

Ar is unsubstituted or substituted phenyl;

R is hydrogen, methyl, heteroaralkyl, (C<sub>3</sub>-C<sub>7</sub> cycloalkyl)alkyl, alkenylalkyl,

H<sub>2</sub>NC(O)alkyl, or C(O)CH<sub>3</sub>;

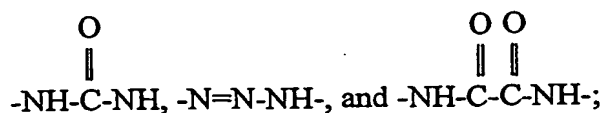
Z is  $\text{-CH}_2\text{-(CH}_2\text{)}_m\text{-}$ ,  $\text{-(CH}_2\text{)}_m\text{-C(=O)-}$ ,  $\text{-O-(CH}_2\text{)}_m\text{-}$ ,  $\text{-(CH}_2\text{)}_m\text{-CH(CH}_3\text{)-}$ ,

$\text{-(CH}_2\text{)}_m\text{-CH(OH)-CH}_2\text{-}$ ,  $\text{-O-C(CH}_3\text{)(O)-}$ ,  $\text{-S-(CH}_2\text{)}_m\text{-}$ ,  $\text{-C}\equiv\text{C-CH}_2\text{-}$ , or  $\text{-C}\equiv\text{C-(CH}_2\text{)}_2\text{-}$

wherein m is an integer 2 or 3;

-E-Y- is selected from  $\text{-O-C(=O)-NH-}$ ,  $\text{-S-C(=O)-NH-}$ ,  $\text{-CH=CH-NH-}$ ,  $\text{-N=CH-NH-}$ ;

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X is hydrogen; and

5 \* denotes *trans*.

Most preferred are compounds of Formula I selected from those listed below:

6-[*trans*-4-(3-Phenylpropylamino)cyclohexyl]-3*H*-benzoxazol-2-one;

6-{*trans*-4-[2-(4-Fluorophenoxy)ethylamino]cyclohexyl}-3*H*-benzoxazol-

10 2-one;

6-[*trans*-4-(2-Phenoxyethylamino)cyclohexyl]-3*H*-benzoxazol-2-one;

6-{*trans*-4-[3-(4-Fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-

2-one;

6-{*cis*-4-[3-(4-Fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-

15 one;

6-[*trans*-4-(2-Phenylsulfanylethylamino)cyclohexyl]-3*H*-benzoxazol-2-

one;

6-[*cis*-4-(2-Phenylsulfanylethylamino)cyclohexyl]-3*H*-benzoxazol-2-one;

6-[4-(3-Phenylpropylamino)cyclohex-1-enyl]-3*H*-benzoxazol-2-one;

20

6-{*trans*-4-[2-(4-Fluorophenylsulfanyl)ethylamino]cyclohexyl}-3*H*-

benzoxazol-2-one;

6-{*trans*-4-[(*R*)-1-Methyl-3-phenylpropylamino]cyclohexyl}-3*H*-

benzoxazol-2-one;

6-{*trans*-4-[(*S*)-1-Methyl-3-phenylpropylamino]cyclohexyl}-3*H*-

25

benzoxazol-2-one;

6-{*trans*-4-[(1*S*,2*S*)-2-Hydroxy-2-(4-methoxyphenyl)-1-

methylethylamino]cyclohexyl}-3*H*-benzoxazol-2-one;

6-{*cis*-4-[(1*S*,2*S*)-2-Hydroxy-2-(4-methoxyphenyl)-1-methylethylamino]-

cyclohexyl}-3*H*-benzoxazol-2-one;

30

6-{*trans*-4-[(1*S*,2*R*)-2-Hydroxy-1-methyl-2-phenylethylamino]-

cyclohexyl}-3*H*-benzoxazol-2-one;

6-[*cis*-4-(3-*p*-Tolylpropylamino)cyclohexyl]-3*H*-benzoxazol-2-one;

6-[*trans*-4-(3-*p*-Tolylpropylamino)cyclohexyl]-3*H*-benzoxazol-2-one;

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6-[*trans*-4-(2-Benzenesulfinylethylamino)cyclohexyl]-3*H*-benzoxazol-2-one;

6-[*trans*-4-(2-Benzenesulfonylethylamino)cyclohexyl]-3*H*-benzoxazol-2-one;

5 6-{*trans*-4-[Methyl(3-phenylpropyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one;

6-(*trans*-4-{[3-(4-Fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;

10 6-(*cis*-4-{[3-(4-Fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;

6-{*trans*-[4-(2-Methyl-3-phenylpropylamino)cyclohexyl]}-3*H*-benzoxazol-2-one

6-{*trans*-4-[Methyl(2-methyl-3-phenylpropyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one;

15 6-{*trans*-[4-(3-Phenyl-prop-2-ynylamino)cyclohexyl]}-3*H*-benzoxazol-2-one;

6-{*trans*-4-[Methyl(3-phenylprop-2-ynyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one;

20 6-{*trans*-4-[2-(4-Fluorophenylsulfanylethyl)methylamino]cyclohexyl}-3*H*-benzoxazol-2-one;

6-{*trans*-4-[3-(4-Trifluoromethylphenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;

6-{*trans*-4-[Methyl-3-(*p*-tolylpropyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one;

25 6-{*trans*-4-[Methyl(2-phenoxyethyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one;

6-{*trans*-4-[Methyl-3-(4-trifluoromethylphenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;

30 6-{*trans*-4-[3-(2,4-Difluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;

6-(*trans*-4-{[3-(2,4-Difluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;

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6-(*trans*-4-{[3-(4-Isopropylphenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;

6-(*trans*-4-{[3-(4-Isobutylphenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;

5 6-(*trans*-4-{[Ethyl-[3-(4-fluorophenyl)propyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one;

6-(*trans*-4-{Ethyl-[3-(4-trifluoromethylphenyl)propyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one;

10 6-(*trans*-4-{Ethyl-[(*R*)-1-methyl-3-phenylpropyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one;

6-(*trans*-4-{Ethyl-[(*S*)-1-methyl-3-phenylpropyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one;

6-{*trans*-4-[[3-(4-Fluorophenyl)propyl]-(2-hydroxyethyl)amino]-cyclohexyl}-3*H*-benzoxazol-2-one;

15 6-(*trans*-4-{Cyclopropylmethyl-[3-(4-fluorophenyl)propyl]-amino}cyclohexyl)-3*H*-benzoxazol-2-one;

6-(*trans*-4-{[3-(4-Fluorophenyl)propyl]furan-3-ylmethylamino}-cyclohexyl)-3*H*-benzoxazol-2-one;

20 6-(*trans*-4-{Allyl-[3-(4-Fluorophenyl)propyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one;

6-(*trans*-4-{[3-(4-Fluorophenyl)propyl]isobutylamino}cyclohexyl)-3*H*-benzoxazol-2-one;

6-(*trans*-4-{(2-Aminoethyl)-[3-(4-fluorophenyl)propyl]amino}-cyclohexyl)-3*H*-benzoxazol-2-one;

25 2-{[3-(4-Fluorophenyl)propyl]-[4-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-cyclohexyl]amino}acetamide;

(*S*)-6-{*trans*-4-[1-(4-Fluorophenylsulfanyl)pentan-2-ylamino]cyclohexyl}-3*H*-benzoxazol-2-one;

30 (*S*)-6-{*trans*-4-[Ethyl(1-(4-fluorophenylsulfanyl)pentan-2-yl)amino]cyclohexyl}-3*H*-benzoxazol-2-one;

6-[*trans*-4-(3-Phenylbutylamino)cyclohexyl]-3*H*-benzoxazol-2-one;

6-[*trans*-4-(Methyl-3-phenylbutylamino)cyclohexyl]-3*H*-benzoxazol-2-one;

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6-{*trans*-4-[3-(4-Chlorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;

6-(*trans*-4-{[3-(4-Chlorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;

5 6-(*trans*-4-{[3-(2,4-Dichlorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;

6-(*trans*-4-[3-(3,5-Difluorophenyl)propylamino]cyclohexyl)-3*H*-benzoxazol-2-one;

10 6-(*trans*-4-{[3-(3,5-Difluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;

6-(*trans*-4-[3-(3,4-Difluorophenyl)propylamino]cyclohexyl)-3*H*-benzoxazol-2-one;

6-(*trans*-4-{[3-(3,4-Difluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;

15 6-(*trans*-4-{[3-(2,3,4-Trifluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;

6-(4-{[3-(*trans*-4-Dimethylaminophenyl)propyl]methylamino}-cyclohexyl)-3*H*-benzoxazol-2-one;

20 6-(*trans*-4-{[3-(2,4,6-Trifluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;

6-(*trans*-4-[3-(2,4-Dimethylphenyl)propylamino]cyclohexyl)-3*H*-benzoxazol-2-one;

6-(*trans*-{4-[Methyl(2,4-dimethylphenylpropyl)amino]cyclohexyl})-3*H*-benzoxazol-2-one;

25 6-{*trans*-4-[3-(2-Chloro-4-fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;

6-(*trans*-4-{[3-(2-Chloro-4-fluorophenyl)propyl]methylamino}-cyclohexyl)-3*H*-benzoxazol-2-one;

30 6-{*trans*-4-[3-(4-Chloro-2-fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;

6-(*trans*-4-{[3-(4-Chloro-2-fluorophenyl)propyl]methylamino}-cyclohexyl)-3*H*-benzoxazol-2-one;

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6-(*trans*-4-[3-(4-Fluoro-2-methylphenyl)propylamino]cyclohexyl)-3*H*-benzoxazol-2-one;

6-(*trans*-{4-[Methyl(4-fluoro-2-methylphenylpropyl)amino]cyclohexyl})-3*H*-benzoxazol-2-one;

5        6-{*trans*-4-[3-(3-Fluoro-2-methylphenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;

6-(*trans*-4-[[3-(3-Fluoro-2-methylphenyl)propyl]methylamino]-cyclohexyl)-3*H*-benzoxazol-2-one;

10       6-{*trans*-4-[3-(2-Fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;

6-(*trans*-4-[[3-(2-Fluorophenyl)propyl]methylamino]cyclohexyl)-3*H*-benzoxazol-2-one;

6-{*trans*-4-[3-(3-Fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;

15       6-(*trans*-4-[[3-(3-Fluorophenyl)propyl]methylamino]cyclohexyl)-3*H*-benzoxazol-2-one;

6-{*trans*-4-[(3-Cyclohexylpropyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one;

20       6-{*trans*-4-[(3-Cyclohexylpropyl)methylamino]cyclohexyl}-3*H*-benzoxazol-2-one;

6-{*trans*-4-[4-(3-Thiophen-3-yl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;

6-[*trans*-4-[[3-(3-Thiophen-3-yl)propyl]methylamino]cyclohexyl]-3*H*-benzoxazol-2-one;

25       6-{*trans*-4-[Methyl(3-thiazol-2-ylpropyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one;

6-(*trans*-4-{Methyl-[2-(methylphenylamino)ethyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one;

30       N-(2-{Methyl-[4-(2-oxo-2,3-dihydrobenzoxazol-6-yl)cyclohexyl]amino}-ethyl)benzamide;

N-{2-[4-(2-Oxo-2,3-dihydrobenzoxazol-6-yl)cyclohexylamino]-ethyl}benzamide;



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6-{*trans*-4-[3-(4-Fluorophenyl)propylamino]cyclohexyl}-3*H*-benzthiazol-2-one;

3-(4-Fluorophenyl)-N-methyl-N-[*trans*-4-(2-oxo-2,3-dihydrobenzoxazol-6-yl)cyclohexyl]propionamide;

5 6-(*trans*-4-{[3-(4-Fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzthiazol-2-one;

5-{*trans*-4-[3-(4-Fluorophenyl)propylamino]cyclohexyl}-1,3-dihydrobenzoimidazol-2-one;

5-(*trans*-4-{[3-(4-Fluorophenyl)propyl]methylamino}cyclohexyl)-1,3-dihydrobenzoimidazol-2-one;

6-(4-{[3-(4-Fluorophenyl)propyl]methyl-amino}cyclohexyl)-5-methyl-3*H*-benzoxazol-2-one; and

6-(*trans*-4-{[3-(4-Fluorophenyl)propyl]methylamino}cyclohexyl)-5-methoxy-3*H*-benzoxazol-2-one.

15 Preferred are compounds of Formula II or pharmaceutically acceptable salts thereof wherein:

X is independently selected from hydrogen or an electron withdrawing group selected from the group consisting of halogen, nitro, cyano, aminoalkyl, CF<sub>3</sub>, C(O)CH<sub>3</sub>, and haloalkyl.

20 More preferred are compounds of Formula II or pharmaceutically acceptable salts thereof wherein:

Ar is unsubstituted or substituted phenyl;

X is independently selected from hydrogen or an electron withdrawing group selected from the group consisting of halogen, nitro, cyano, aminoalkyl, CF<sub>3</sub>, C(O)CH<sub>3</sub>, and haloalkyl; and

-E-Y- is selected from  $\text{-O-C(=O)-NH-}$ ,  $\text{-S-C(=O)-NH-}$ ,  $\text{-CH=CH-NH-}$ ,  $\text{-N=CH-NH-}$ ;

$\text{-NH-C(=O)-NH-}$ ,  $\text{-N=N-NH-}$ , and  $\text{-NH-C(=O)-C(=O)-NH-}$ ; and

\* denotes *trans*.

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Still more preferred are compounds of Formula II or pharmaceutically acceptable salts thereof wherein:

Ar is unsubstituted or substituted phenyl;

Ar and the nitrogen atom bearing R are separated by 3 or 4 atoms;

5 X is independently selected from hydrogen or an electron withdrawing group selected from the group consisting of halogen, nitro, cyano, CF<sub>3</sub>, C(O)CH<sub>3</sub>, and haloalkyl;

10 -E-Y- is selected from  $\begin{array}{c} \text{O} \\ \parallel \\ -\text{O}-\text{C}-\text{NH}- \end{array}$ ,  $\begin{array}{c} \text{O} \\ \parallel \\ -\text{S}-\text{C}-\text{NH}- \end{array}$ ,  $-\text{CH}=\text{CH}-\text{NH}-$ ,  $-\text{N}=\text{CH}-\text{NH}-$ ;

$\begin{array}{c} \text{O} \\ \parallel \\ -\text{NH}-\text{C}-\text{NH}- \end{array}$ ,  $\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ -\text{N}=\text{N}-\text{NH}- \end{array}$ , and  $\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ -\text{NH}-\text{C}-\text{C}-\text{NH}- \end{array}$ ; and

\* denotes *trans*.

15 Still more preferred are compounds of Formula II or pharmaceutically acceptable salts thereof wherein:

Ar is unsubstituted or substituted phenyl;

T is

20  $\begin{array}{c} \text{H} \quad \text{R}_1 \quad \text{O} \\ | \quad | \quad \parallel \\ (\text{A})_{0-1}-\text{N}-\text{C}-\text{C}- \\ | \\ \text{R}_2 \end{array}$ ,  $\begin{array}{c} \text{H} \quad \text{R}_1 \quad \text{O} \\ | \quad | \quad \parallel \\ (\text{A})_{0-1}-\text{N}-\text{CH}_2-\text{C}-\text{C}- \\ | \\ \text{R}_2 \end{array}$ ,  $\begin{array}{c} \text{H} \quad \text{O} \quad \text{R}_1 \\ | \quad \parallel \quad | \\ (\text{A})_{0-1}-\text{N}-\text{C}-\text{C}- \\ | \\ \text{R}_2 \end{array}$ ,  $\begin{array}{c} \text{H} \quad \text{O} \quad \text{R}_1 \\ | \quad \parallel \quad | \\ (\text{A})_{0-1}-\text{N}-\text{C}-\text{C}-\text{CH}_2- \\ | \\ \text{R}_2 \end{array}$ ,

25  $\begin{array}{c} \text{H} \quad \text{R}_1 \\ | \quad | \\ -(\text{A})_{0-1}-\text{N}-\text{C}-\text{CH}_2- \\ | \\ \text{R}_2 \end{array}$ ,  $\begin{array}{c} \text{H} \quad \text{R}_1 \\ | \quad | \\ (\text{A})_{0-1}-\text{N}-\text{CH}_2-\text{C}-\text{CH}_2- \\ | \\ \text{R}_2 \end{array}$ ,  $\begin{array}{c} \text{H} \quad \text{R}_1 \\ | \quad | \\ (\text{A})_{0-1}-\text{N}-\text{CH}_2-\text{C}- \\ | \\ \text{R}_2 \end{array}$ ; or

30  $\begin{array}{c} \text{H} \quad \text{R}_1 \\ | \quad | \\ -(\text{A})_{0-1}-\text{N}-\text{CH}_2-\text{C}-\text{CH}_2- \\ | \\ \text{R}_2 \end{array}$ ;

R is hydrogen or methyl or heteroaralkyl or (C<sub>3</sub>-C<sub>7</sub> cycloalkyl) alkyl;

35 H<sub>2</sub>NC(O)alkyl, alkenylalkyl, or C(O)CH<sub>3</sub>;

X is hydrogen; and

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-E-Y- is selected from  $\text{-O-C(=O)-NH-}$ ,  $\text{-S-C(=O)-NH-}$ ,  $\text{-CH=CH-NH-}$ ,  $\text{-N=CH-NH-}$ ;

5

$\text{-NH-C(=O)-NH-}$ ,  $\text{-N=N-NH-}$ , and  $\text{-NH-C(=O)-C(=O)-NH-}$ ; and

\* denotes *trans*.

Preferred compounds of Formula II are:

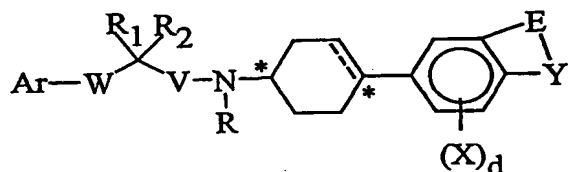
6-[*trans*-4-(2-Phenylaminoethylamino)cyclohexyl]-3*H*-benzoxazol-2-one;

10

and

N-(2-{Methyl[4-(2-oxo-2,3-dihydrobenzoxazol-6-yl)cyclohexyl]amino}-ethyl)benzamide.

Another preferred compound is that of Formula III



III

15

with the substituents as described above for Formula I.

Other preferred compounds of Formula III are:

Ar is unsubstituted or substituted phenyl;

X is independently selected from hydrogen or an electron withdrawing group selected from the group consisting of halogen, nitro, cyano, aminoalkyl,  $\text{CF}_3$ ,  $\text{C(O)CH}_3$ , and haloalkyl; and

20

-E-Y- is selected from  $\text{-O-C(=O)-NH-}$ ,  $\text{-S-C(=O)-NH-}$ ,  $\text{-CH=CH-NH-}$ ,  $\text{-N=CH-NH-}$ ;

25

$\text{-NH-C(=O)-NH-}$ ,  $\text{-N=N-NH-}$ , and  $\text{-NH-C(=O)-C(=O)-NH-}$ ; and

\* denotes *cis* or *trans*.

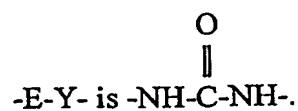
Other preferred compounds are compounds of Formula I, Formula II, or Formula III wherein:

30

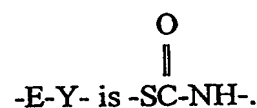
-E-Y- is  $\text{-O-C(=O)-NH-}$ .

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Other preferred compounds are compounds of Formula I, Formula II, or Formula III wherein:



Other preferred compounds are compounds of Formula I, Formula II, or Formula III wherein:



Preferably the pharmaceutical compositions are useful for the treatment of the neurodegenerative disorder Parkinson's disease.

Preferably, the pharmaceutical compositions are useful as a dopamine against or precursor thereof in amount effective to treat Parkinson's disease.

15       Other preferred compounds are those where \* denotes *cis*.

The diradical group E-Y must contain a hydrogen bond donor functionality.

The term "alkyl" means a straight or branched hydrocarbon radical having from 1 to 12 carbon atoms unless otherwise specified, also known as a C<sub>1</sub>-C<sub>12</sub> alkyl, and includes, for example, methyl, ethyl, 1-propyl, and 2-propyl, 1-butyl, 2-butyl, 2-methyl-1-propyl, 1,1-dimethylethyl, 1-pentyl, 2-pentyl, 3-pentyl, 2,2-dimethylpropyl, 1-hexyl, 2-hexyl, 3-hexyl, 4-methyl-1-pentyl, 1-heptyl, 2-heptyl, 3-heptyl, 4-heptyl, 5-methyl-1-hexyl, 1-octyl, 2-octyl, 3-octyl, 4-octyl, 6-methyl-1-heptyl, 5,5-dimethylhexyl, 1-nonyl, 2-nonyl, 1-decyl, 2-decyl, 25       1-undecyl, 2-undecyl, 1-dodecyl, and 5-dodecyl. Alkyl groups may be unsubstituted or independently substituted by from 1 to 3 substituents selected from F, Cl, Br, I, OH, NH<sub>2</sub>, SH, CN, NO<sub>2</sub>, OCH<sub>3</sub>, OC(O)CH<sub>3</sub>, CF<sub>3</sub>, OCH<sub>2</sub>CH<sub>2</sub>OH, NHC(O)CH<sub>3</sub>, NHCH<sub>3</sub>, or N(CH<sub>3</sub>)<sub>2</sub>.

30       Alkyl groups having two or more carbons may optionally contain 1 or 2 sites of unsaturation, the groups being known as alkenyl groups or radicals. Illustrative examples of an alkenyl group or radical having from 2 to 12 carbon atoms, also known as a C<sub>2</sub>-C<sub>12</sub> alkenyl, include ethenyl, 1-propenyl, 2-propenyl, 1-buten-1-yl, 2-buten-1-yl, 1-penten-1-yl, 2-penten-1-yl, 1-penten-3-yl, 1-penten-

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5-yl, 1-hexen-1-yl, 1-hexen-4-yl, 2-hexen-1-yl, 3-hexen-1-yl, 2-octen-3-yl, 5-nonen-2-yl, 4-undecen-4-yl, and 5-dodecen-2-yl.

The term "aryl" means an aromatic carbocyclic ring having from 6 to 10 carbon atoms. Illustrative examples of an aryl group or radical include phenyl, 1-naphthyl, and 2-naphthyl. Aryl groups may be unsubstituted or independently substituted by from 1 to 3 substituents selected from F, Cl, Br, I, OH, NH<sub>2</sub>, SH, CN, NO<sub>2</sub>, OCH<sub>3</sub>, OC(O)CH<sub>3</sub>, CF<sub>3</sub>, OCH<sub>2</sub>CH<sub>2</sub>OH, NHC(O)CH<sub>3</sub>, NHCH<sub>3</sub>, or N(CH<sub>3</sub>)<sub>2</sub>.

The term "aralkyl" means an aryl-alkyl- group or radical wherein aryl and alkyl have the meanings as defined above. Illustrative examples of an arylalkyl group or radical include benzyl, 4-fluorophenylmethyl, 2-phenylethyl, 3-phenylpropyl, 4-phenylbutyl, 3-methyl-3-phenylpropyl, 1-naphthylmethyl, 1-naphthylethyl, 3-(1-naphthyl)-propyl, 4-(1-naphthyl)-butyl, 4-(2-naphthyl)-butyl, 4-phenylheptyl, and 12-(2-hydroxyphenyl)-dodec-3-yl.

The term "(C<sub>3</sub>-C<sub>7</sub> cycloalkyl)-alkyl" means an "alkyl" group (as described above) substituted thereon by a cycloalkyl group of from 3 to 7 carbon atoms such as cyclopentyl, cyclopropyl, cyclohexyl, or cycloheptyl.

The term "heteroatom" means nitrogen, oxygen, or sulfur.

The term "heteroaryl" means an unsaturated monocyclic group or radical of 5 or 6 atoms, an unsaturated fused bicyclic group or radical of from 8 to 10 atoms, or an unsaturated fused tricyclic group or radical of from 11 to 14 atoms, the cyclic groups having 1 or 2 heteroatoms independently selected from O, N, or S. Heteroaryl does not contain a hydrogen bond donor diradical group E-Y. Illustrative examples of monocyclic heteroaryl include 2- or 3-thienyl, 2- or 3-furanyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, 2-, 4-, or 5-oxazolyl, 2-, 4-, or 5-thiazolyl, 3-, 4-, or 5-isoxazolyl, 3-, 4-, or 5-isothiazolyl, 2-, 3-, or 4-pyridinyl, 3- or 4-pyridazinyl, 2- or 3-pyrazinyl, and 2-, 4- or 5-pyrimidinyl. Illustrative examples of bicyclic heteroaryl include 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl, 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolinyl, 1-indolyl, 2-, 3-, 4-, 5-, 6-, or 7-benzo[b]thienyl, 2-, 4-, 5-, 6-, or 7-benzofuran, 2-, 4-, 5-, 6-, or 7-benzoxazolyl, 2-, 4-, 5-, 6-, or 7-benzothiazolyl, and 1-benzimidazolyl. Illustrative examples of tricyclic heteroaryl include 1-, 2-, 3-, or 4-dibenzofuranyl, 1-, 2-, 3-, or

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4-dibenzothienyl and 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, or 9-(1,2,3,4-tetrahydroacridinyl). All with the proviso that when Z in Formula I is attached via a heteroatom, Z is attached to a carbon atom of the heteroaryl group or radical. Heteroaryl groups may be unsubstituted or independently substituted by from 1 to 3 substituents selected from F, Cl, Br, I, OH, NH<sub>2</sub>, SH, CN, NO<sub>2</sub>, OCH<sub>3</sub>, OC(O)CH<sub>3</sub>, CF<sub>3</sub>, OCH<sub>2</sub>CH<sub>2</sub>OH, NHC(O)CH<sub>3</sub>, NHCH<sub>3</sub>, or N(CH<sub>3</sub>)<sub>2</sub>.

As used above, a fused bicyclic group or radical is a group wherein 2 ring systems share two and only 2 atoms.

As used above, a fused tricyclic group or radical is a group wherein 3 ring systems share four and only 4 atoms.

“—” denotes a single or double bond.

The term “heteroaralkyl” means a heteroaryl-alkyl- group or radical wherein heteroaryl and alkyl have the meanings as defined above. Illustrative examples of an heteroaralkyl group or radical include 4-pyridyl-methyl, (4-fluoroquinolin-2-yl)methyl, 2-(isoxazol-3-yl)ethyl, and 12-(5-chlorothiophen-2-yl)-dodec-3-yl.

The term “halogen” means bromine, chlorine, fluorine, or iodine. The term “aminoalkyl” means an H<sub>2</sub>N-alkyl- group or radical wherein alkyl has the meaning as defined above, which is a substituted alkyl group or radical containing from 1 to 3 substituents wherein at least one substituent is -NH<sub>2</sub>.

The term “hydroxyalkyl” means an HO-alkyl- group or radical wherein alkyl has the meaning as defined above, which is a substituted alkyl group or radical containing from 1 to 3 substituents wherein at least 1 substituent is -OH.

The term “amino(hydroxy)alkyl” means an H<sub>2</sub>N(HO)-alkyl- group or radical wherein alkyl has the meaning as defined above, which is a substituted alkyl group or radical containing from 2 or 3 substituents wherein at least 1 substituent is OH and 1 substituent is -NH<sub>2</sub>.

The term “(aminocarbonyl)alkyl” means an H<sub>2</sub>NC(O)-alkyl- group or radical wherein alkyl has the meaning as defined above, which is a substituted alkyl group or radical containing from 1 to 3 substituents wherein at least 1 substituent is -(O)C-NH<sub>2</sub>.

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The term "thioalkyl" means an HS-alkyl- group or radical wherein alkyl has the meaning as defined above, which is a substituted alkyl group or radical containing from 1 to 3 substituents wherein at least 1 substituent is -SH.

The term "alkenylalkyl" means a (C<sub>2</sub>-C<sub>12</sub> alkenyl)-(C<sub>1</sub>-C<sub>12</sub> alkyl) group or radical wherein C<sub>2</sub>-C<sub>12</sub> alkenyl and C<sub>1</sub>-C<sub>12</sub> alkyl are as defined above.

The term "(methylthio)-alkyl-" means an CH<sub>3</sub>S-alkyl- group or radical wherein alkyl has the meaning as defined above, which is a substituted alkyl group or radical containing from 1 to 3 substituents wherein at least 1 substituent is -SCH<sub>3</sub>.

The term "carboxyalkyl" means an HO<sub>2</sub>C-alkyl- group or radical wherein alkyl has the meaning as defined above, which is a substituted alkyl group or radical containing from 1 to 3 substituents wherein at least one substituent is -CO<sub>2</sub>H.

The term "haloalkyl" means a halogen-alkyl- group or radical wherein halogen and alkyl have the meanings as defined above, which is a substituted alkyl group or radical containing from 1 to 3 substituents wherein at least 1 substituent is selected from F, Cl, Br, or I.

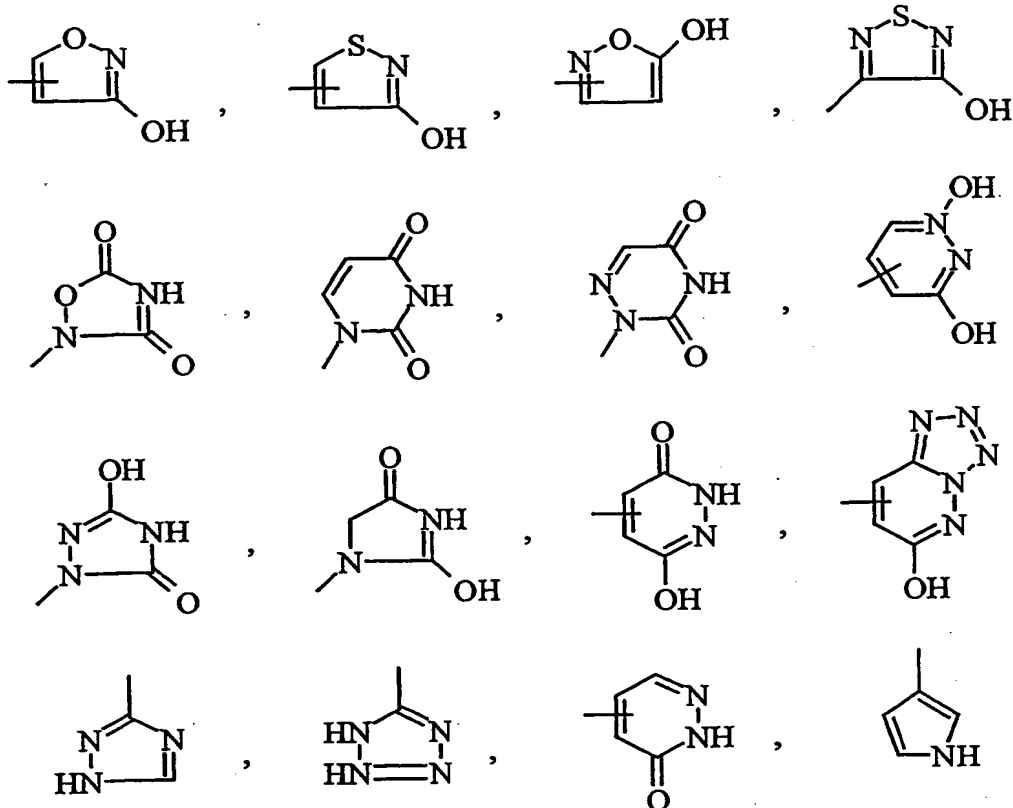
The term "ureidoalkyl" means an H<sub>2</sub>N-(C=O)-NH-alkyl- group or radical wherein alkyl has the meanings as defined above, which is a substituted alkyl group or radical containing from 1 to 3 substituents wherein at least 1 substituent is H<sub>2</sub>N-(C=O)-NH-.

The term "electron withdrawing group" means a group or radical selected from halogen, nitro, cyano, alkyl, CF<sub>3</sub>, C(O)CH<sub>3</sub>, P(O)(O-R<sub>9</sub>)<sub>2</sub>, SO<sub>2</sub>-R<sub>9</sub>, SO<sub>2</sub>NHR<sub>9</sub>, C(O)NR<sub>9</sub>R<sub>9</sub>', wherein R<sub>9</sub> is independently selected from C<sub>1</sub>-C<sub>6</sub> alkyl or unsubstituted or substituted phenyl, -(C=NH)-NH<sub>2</sub>, -(C=NH)-O-alkyl, methoxymethyl, or haloalkyl, wherein the substituents may be F, Cl, Br, I, OH, NH<sub>2</sub>, SH, CN, NO<sub>2</sub>, OCH<sub>3</sub>, OC(O)CH<sub>3</sub>, CF<sub>3</sub>, OCH<sub>2</sub>CH<sub>2</sub>OH, NHC(O)CH<sub>3</sub>, NHCH<sub>3</sub>, or N(CH<sub>3</sub>)<sub>2</sub>.

The phrase "heterocycle, which heterocycle is a carboxylic acid or an amide isostere" means a 5- or 6-membered monocyclic ring containing from 1 to 4 heteroatoms selected from N, O, and S and providing a hydrogen bond

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donor moiety selected from NH, OH, and SH. Illustrative examples include the following structures:



5

See also Greenwood J.R., Vaccarella G., Cooper H.R., Allan R.D., Johnston G.A.R., *Internet Journal of Chemistry*, 1998;1(38)(Chart 4). Additional examples are well-known to the skilled artisan. (See, for example, (i) Lipinski C.A., *Annual Reports in Medicinal Chemistry*, 1986;21:Chaps 21, 27;

10 (ii) Thornber C.W., *Chem. Soc. Rev.*, 1979;8:563; (iii) Burger A., *Progress in Drug Research*, 1991;37:288-371.

The term "entgegen" means the stereoisomerism about a carbon-carbon double bond wherein the highest ranking substituent on each carbon are on opposite sides, which substituent ranking is based on the sequence rules of the

15 Cahn-Ingold-Prelog system (March J., *Advanced Organic Chemistry*, 4<sup>th</sup> ed., New York: John Wiley & Sons 1992:109, 127 and references cited therein).

The term "zusammen" means the stereoisomerism about a carbon-carbon double bond wherein the highest ranking substituent on each carbon are on the



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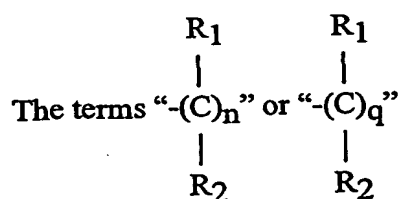
same side, which substituent ranking is based on the sequence rules of the Cahn-Ingold-Prelog system (March J., *supra*, 1992).

The term "*cis*" means the stereoisomerism about a carbon-carbon double bond, a monocyclic ring, a fused bicyclic ring, or a bridged bicyclic ring wherein the highest ranking substituent on each of the two carbons of relevance are on the same side, which substituent ranking is based on the sequence rules of the Cahn-Ingold-Prelog system (March J., *supra*, 1992).

The term "*trans*" means the stereoisomerism about a carbon-carbon double bond, a monocyclic ring, a fused bicyclic ring, or a bridged bicyclic ring wherein the highest ranking substituent on each of the two carbons of relevance are on opposite sides, which substituent ranking is based on the sequence rules of the Cahn-Ingold-Prelog system (March J., *supra*, 1992).

The terms "*cis*" or "*trans*" refers to the relative stereochemistry of the groups attached to the cyclohexyl rings of Formulas I or II at the carbon atoms denoted by "\*".

The term "(X)<sub>d</sub>" means the group X is present 1 or 2 times on the phenylene to which it is attached, which group is independently selected from hydrogen or an electron withdrawing group wherein the electron withdrawing group is as defined above unless otherwise stated. The groups X can be the same or different.



wherein n is an integer of from 1 to 6 and q is an integer of from 0 to 6 mean a chain of from 1 to 6 carbons or from 0 to 6 carbons, respectively, wherein each carbon is independently substituted, which substituents are the groups R<sub>1</sub> and R<sub>2</sub>, wherein R<sub>1</sub> and R<sub>2</sub> are independently (R<sub>1</sub> and R<sub>2</sub> in each occurrence can be the same or different) selected from the groups consisting of hydrogen, alkyl, OH, hydroxyalkyl, aminolalkyl, aralkyl, or N(R<sub>4</sub>)(R<sub>5</sub>) wherein R<sub>4</sub> and R<sub>5</sub> are independently selected from hydrogen, alkyl, aralkyl, heteroaryl, heteroaralkyl,

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aminoalkyl, hydroxyalkyl and thioalkyl, unless otherwise stated. The groups  $R_1$  can be the same or different and the groups  $R_2$  can be the same or different.

The group -E-Y-, together with the phenyl to which it is attached, is a bicycle that contains a hydrogen bond donor functionality.

5 For purposes of the syntheses of the compounds of the present invention, reactive functional groups present in starting materials, reaction intermediates, or reaction products may be protected during chemical reactions using protecting groups which render the reactive functional groups substantially inert to the reaction conditions (see, for example, Green T., Wuts P.G., *Protective Groups in*  
10 *Organic Synthesis*, 2nd ed., New York: John Wiley & Sons, 1991). Thus, for example, protecting groups such as the following may be utilized to protect suitable amino, hydroxyl, and other groups of related reactivity: carboxylic acyl groups, such as formyl, acetyl, trifluoroacetyl; alkoxycarbonyl groups, such as ethoxycarbonyl, *t*-butoxycarbonyl (BOC),  $\beta,\beta,\beta$ -trichloroethoxycarbonyl (TCEC),  
15  $\beta$ -iodoethoxycarbonyl; aryloxycarbonyl groups, such as benzyloxycarbonyl, *p*-methoxybenzyloxycarbonyl, phenoxycarbonyl; trialkyl silyl groups, such as trimethylsilyl and *t*-butyldimethylsilyl (TBDMS); and groups such as trityl, tetrahydropyranyl, vinyloxycarbonyl, *o*-nitrophenylsulfenyl, diphenylphosphinyl, *p*-toluenesulfonyl, and benzyl may all be utilized. The protecting group may be  
20 removed, after completion of the synthetic reaction of interest, by procedures known to those skilled in the art. For example, a BOC group may be removed by acidolysis, a trityl group by hydrogenolysis, TBDMS by treatment with fluoride ions, and TCEC by treatment with  $Zn$

25 Certain of the compounds of the present invention possess one or more chiral centers and each center may exist in the R or S configuration. The present invention includes all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. Additionally, the compounds of the present invention may exist as geometric isomers. The present invention includes all *cis*, *trans*, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the  
30 appropriate mixtures thereof.

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Some of the compounds of Formula I-III are capable of further forming pharmaceutically acceptable acid-addition and/or base salts. All of these forms are within the scope of the present invention.

Pharmaceutically acceptable acid addition salts of the compounds of Formula I-III include salts derived from nontoxic inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydroiodic, hydrofluoric, phosphorous, and the like, as well as the salts derived from nontoxic organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanolic acids, hydroxy alkanolic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinates suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate (see, for example, Berge S.M., et al., *Journal of Pharmaceutical Science*, 1977;66:1-19).

The acid addition salt of said basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner.

Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are N,N-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine (see, for example, Berge, supra., 1977).

The base addition salts of said acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner.

Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated

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forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. Thus, the compounds of the present invention can be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds of the present invention can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either a compound of Formula I-III or a corresponding pharmaceutically acceptable salt of a compound of Formula I-III.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from 5% or 10% to about 70% of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

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For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted, and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing, and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations, which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 to 100 mg preferably 0.5 to 100 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

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In therapeutic use as antagonists or as agents for the treatment of diseases, the compounds utilized in the pharmaceutical method of this invention are administered at the initial dosage of about 0.01 to about 100 mg/kg daily. A daily dose range of about 0.01 to about 10 mg/kg is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages, which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

Tablet Formulation

Ingredient	Amount (mg)
Example 1	25
Lactose	50
Cornstarch (for mix)	10
Cornstarch (for paste)	10
Magnesium stearate (1%)	5
Total	100

Example 1, lactose and cornstarch (for mix) are blended to uniformity. The cornstarch (for paste) is suspended in 200 mL of water and heated with stirring to form a paste. The paste is used to granulate the mixed powders. The wet granules are passed through a No. 8 hand screen and dried at 80°C. The dry granules are lubricated with the 1% magnesium stearate and pressed into a tablet. Such tablets can be administered to a human from one to four times a day for treatment of disease caused by over excitation of NMDA receptor channel complexes.

The compounds of the present invention can be prepared according to the various synthetic schemes that follow. Protecting groups may be used when

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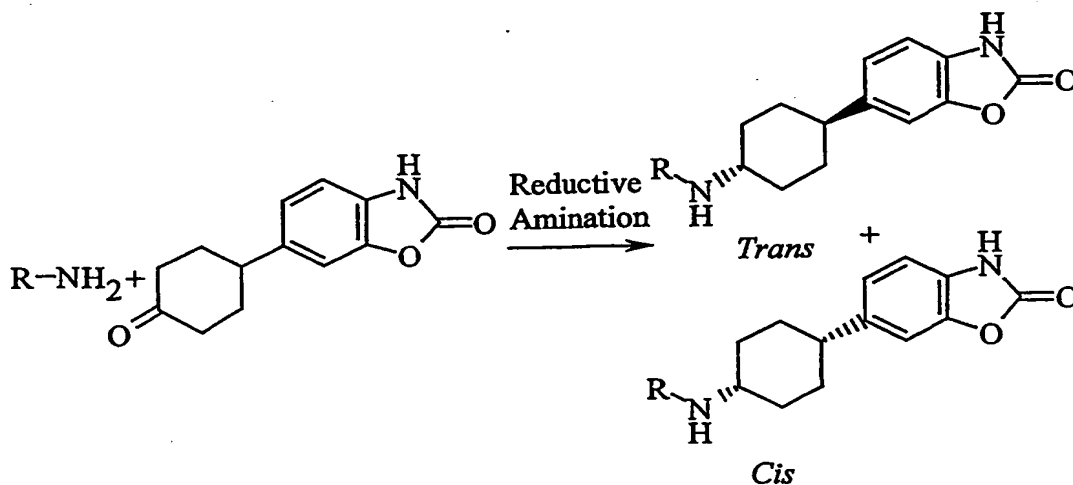
appropriate throughout many of the schemes. Although specifically noted in certain schemes, the appropriate use and choice of protecting groups is well known by one skilled in the art, and is not limited to the specific examples below. It is also understood that such groups not only serve to protect chemically reactive sites, but also to enhance solubility or otherwise change physical properties. A good general reference for protecting group preparation and deprotection is "Protective Groups in Organic Synthesis" (Green T., supra., 1991). A number of general reactions such as oxidations and reductions are not shown in detail but can be done by methods understood by one skilled in the art. General transformations are well-reviewed in "Comprehensive Organic Transformation" by Richard Larock, and the series "Compendium of Organic Synthetic Methods" published by Wiley-Interscience, 1989. In general, the starting materials were obtained from commercial sources unless otherwise indicated.

## PREPARATION OF COMPOUNDS

### Benzoxazolines

In general, these compounds can be prepared by a reductive amination reaction between an amine and 6-(4-cyclohexanonyl)benzoxazolin-2-one 5 (Scheme 1). A synthetic procedure for the synthesis of 5 is shown in Scheme 2.

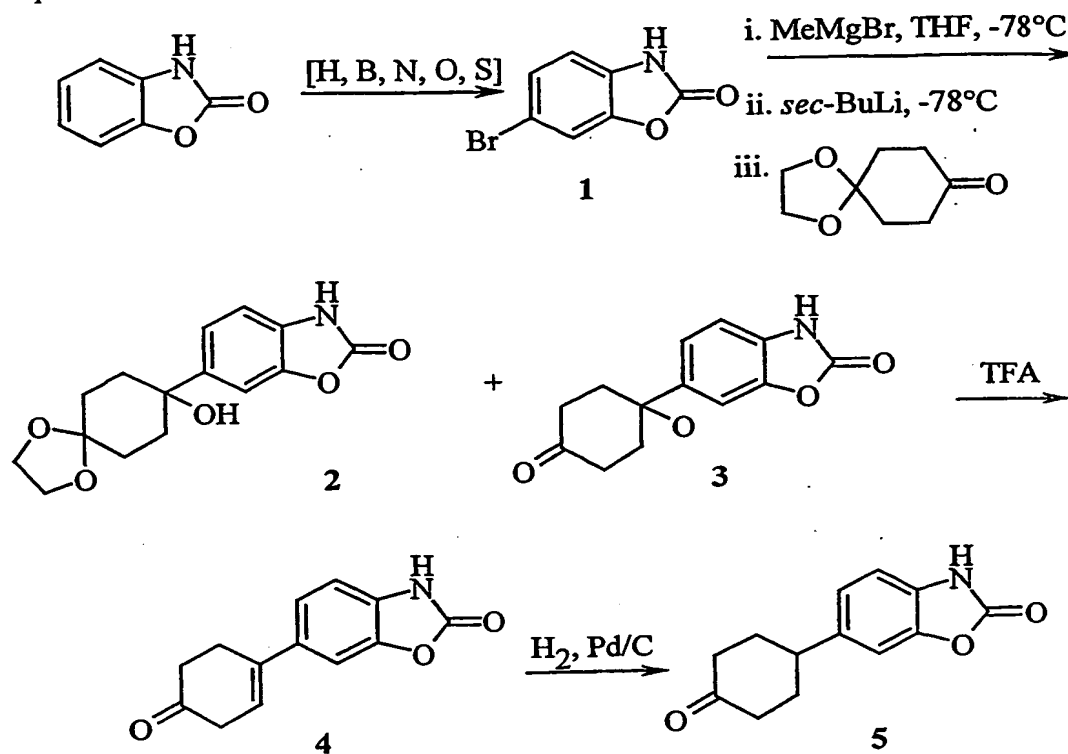
Scheme 1



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## Scheme 2

## Preparation of 6-(4-Cyclohexanonyl)benzoxazolin-2-one 5



**Step 1:** *N*-Bromosuccinimide (26.6 g, 0.15 mol) was added to a stirred solution of 2-benzoxazolinone (20.0 g, 0.15 mol) in glacial acetic acid (220 mL), and the mixture was stirred at room temperature for 3 days. The reaction mixture was poured into  $\text{H}_2\text{O}$  (1.2 L), and the white solid that formed was collected.

Recrystallization from hot EtOH (300 mL) gave bromide 1 (22.1 g, 70%) as an off-white solid: mp  $190\text{--}195^{\circ}\text{C}$ ; IR (KBr):  $3278, 1779, 1736, 1623\text{ cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.41 (d,  $J = 2\text{ Hz}$ , 1H), 7.32 (dd,  $J = 5, 2\text{ Hz}$ , 1H), 6.99 (d,  $J = 5\text{ Hz}$ , 1H); CI MS (methane) ( $m/z$ ): 215  $[\text{M} + \text{H}]^+$ .

**Step 2:** Bromide 1 (12.8 g, 59.6 mmol) was dissolved in anhydrous THF (220 mL), and the solution was cooled to  $-78^{\circ}\text{C}$ . Solutions of MeMgBr (21.9 mL of a 3.0 M solution in  $\text{Et}_2\text{O}$ , 65.6 mmol), *sec*-BuLi (50.4 mL of a 1.3 M solution in cyclohexane, 65.6 mmol), and 1,4-cyclohexanedione mono-ethylene ketal (11.2 g, 71.5 mmol) in anhydrous THF (10 mL) were added sequentially at



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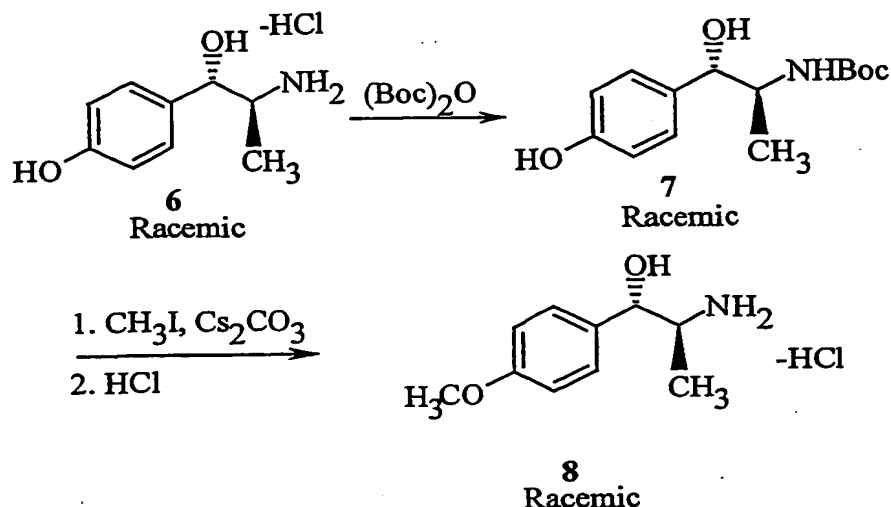
30-minute intervals. After the final addition, the reaction mixture was allowed to warm to room temperature. The reaction was quenched by the addition of 1N HCl (25 mL). The reaction mixture was diluted with EtOAc (500 mL), washed with saturated NaCl (250 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure to provide a mixture of 2 and 3, as a brown oil.

Step 3: The crude product from Step 2 was stirred in TFA (20 mL) at room temperature for 20 minutes. The red solution was poured into CHCl<sub>3</sub> (500 mL) and the organic layer was washed with H<sub>2</sub>O (2 × 100 mL), saturated NaHCO<sub>3</sub>, and saturated NaCl, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure. Purification by filtration through silica gel (eluent 9:1 CHCl<sub>3</sub>/MeOH) gave a yellow oil. Crystallization from hexanes:EtOAc (3:1) gave 4 (8.1 g, 59%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.40 (d, *J* = 1 Hz, 1H), 7.30 (dd, *J* = 8, 1 Hz, 1H), 7.06 (d, *J* = 8 Hz, 1H), 6.11 (t, *J* = 4 Hz, 1H), 3.01 (d, *J* = 2 Hz, 2H), 2.83 (t, *J* = 7 Hz, 2H), 2.53 (m, 2H); CI MS (methane) (*m/z*): 230 [M + H]<sup>+</sup>.

Step 4: A mixture of 4 (3.5 g, 15.3 mmol) in a 3:2 mixture of EtOAc/EtOH (100 mL) and 10% Pd/C (0.5 g) was shaken under a H<sub>2</sub> atmosphere at 50 psi for 4 hours. The solution was filtered through Celite and concentrated under reduced pressure. Crystallization from hexanes:EtOAc (3:1) gave 6-(4-cyclohexanonyl)benzoxazolin-2-one 5 (3.45 g, 98%) as a white solid: mp 202-211°C; IR (KBr): 3339, 1777, 1713, 1618 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.26 (s, 1H), 7.08 (d, *J* = 8 Hz, 1H), 7.01 (d, *J* = 8 Hz, 1H), 3.08 (tt, *J* = 14, 4 Hz, 1H), 2.63-2.51 (m, 2H), 2.24 (br d, *J* = 14 Hz, 2H), 2.07-2.02 (m, 2H), 1.95-1.85 (dddd, *J* = 14, 14, 14, 4 Hz, 2H).

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## Scheme 3

Preparation of  $\alpha$ -(1-Aminoethyl)-4-methoxybenzyl alcohol hydrochloride 8

**Step 1:** To a stirred suspension of  $\alpha$ -(1-aminoethyl)-4-hydroxybenzyl alcohol hydrochloride 6 (5.0 g, 25 mmol), at  $0^\circ\text{C}$ , in  $\text{CH}_2\text{Cl}_2$  (100 mL) was added  $\text{Et}_3\text{N}$  (10.6 mL, 76 mmol) followed by  $(\text{Boc})_2\text{O}$  (5.9 g, 27 mmol). The reaction mixture was warmed to room temperature and stirred for 2 hours. The reaction mixture was washed with 2N HCl ( $2 \times 50$  mL). The organic layer was separated, and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic solutions were washed with saturated NaCl, dried ( $\text{Na}_2\text{SO}_4$ ), and filtered. Concentration under reduced pressure gave 7 (7.01 g, 93%) which was used without further purification.

**Step 2:** To a solution of 7 (7.0 g, 23 mmol) in acetone (120 mL) was added  $\text{K}_2\text{CO}_3$  (10.2 g, 73 mmol) followed by MeI (3.3 mL, 52 mmol). The reaction mixture was heated under reflux, under a  $\text{N}_2$  atmosphere for 15 hours. After cooling to room temperature, the reaction mixture was filtered off, and the filtrate was concentrated under reduced pressure. Purification by flash chromatography (silica, 95:5  $\text{CH}_2\text{Cl}_2$ :MeOH) and (silica, 1:4 EtOAc:hexanes) afforded 3.0 g (41%) of desired material, which was used without further purification:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.25 (d,  $J = 7$  Hz, 2H), 6.88 (d,

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$J = 7$  Hz, 2H), 4.80–4.75 (m, 1H), 4.60–4.54 (br s, 1H), 4.00–3.93 (br s, 1H), 3.80 (s, 3H), 3.12–3.04 (br s, 1H), 1.46 (s, 9H), 0.99 (d,  $J = 7$  Hz, 3H).

Step 3: The carbamate 7 (3.0 g, 9.4 mmol) was stirred in HCl (25 mL of a 4 M solution in dioxane, 100 mmol) for 3 hours. The reaction mixture was then diluted with Et<sub>2</sub>O, which resulted in a white precipitate that was collected by filtration and dried to yield the desired amine 8 as the HCl salt (1.3 g, 54%): <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD):  $\delta$  7.32 (d,  $J = 9$  Hz, 2H), 6.94 (d,  $J = 9$  Hz, 2H), 4.85 (s, 1H), 3.79 (s, 3H), 3.49–3.45 (m, 1H), 1.25 (d,  $J = 7$  Hz, 3H).

### Reductive Amination

#### General Methods

HCl salts were prepared by treatment of a MeOH solution of the amine with excess HCl in Et<sub>2</sub>O (1.0 M). The salts were isolated either by filtration, if they precipitated directly from the etherial solution, or by first removal of the solvent under reduced pressure, and then crystallization (Et<sub>2</sub>O/MeOH).

Purity was determined by reversed phase HPLC by the following methods:

Method A: column: YMC J'Sphere C18, ODS-M80, 150 × 4.6 mm, 4  $\mu$ ; solvent A: 0.1% H<sub>3</sub>PO<sub>4</sub> in H<sub>2</sub>O; solvent B: 0.1% H<sub>3</sub>PO<sub>4</sub> in CH<sub>3</sub>CN; gradient: 10% to 100% B over 15 minutes; flow: 1 mL min<sup>-1</sup>; detection: 210 nm.

Method B: column: YMC J'Sphere C18, ODS-M80, 150 × 4.6 mm, 4  $\mu$ ; solvent A: 0.1% H<sub>3</sub>PO<sub>4</sub> in H<sub>2</sub>O; solvent B: 0.1% H<sub>3</sub>PO<sub>4</sub> in MeOH; gradient: 10% to 100% B over 15 minutes; flow: 1 mL min<sup>-1</sup>; detection: 210 nm.

Method C: column: Dynamax 300Å C18, 250 × 4.6 mm + guard, 5  $\mu$ ; solvent A: 0.1% H<sub>3</sub>PO<sub>4</sub> in H<sub>2</sub>O; solvent B: 0.1% H<sub>3</sub>PO<sub>4</sub> in CH<sub>3</sub>CN; gradient: 10% to 100% B over 25 minutes; flow: 1 mL min<sup>-1</sup>; detection: 215 nm.

Method D: column: Dynamax 300Å C18, 250 × 4.6 mm + guard, 5  $\mu$ ; solvent A: 0.1% H<sub>3</sub>PO<sub>4</sub> in H<sub>2</sub>O; solvent B: 0.1% H<sub>3</sub>PO<sub>4</sub> in MeOH; gradient: 10% to 100% B over 30 minutes; flow: 1 mL min<sup>-1</sup>; detection: 215 nm.

Method E: column: YMC J'Sphere C18, ODS-M80, 150 × 4.6 mm, 4  $\mu$ ;

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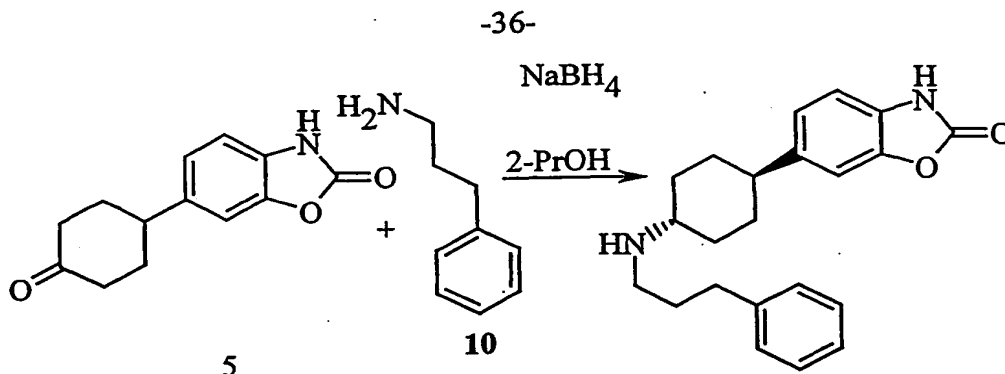
solvent A: 0.1% formic acid in H<sub>2</sub>O; solvent B: 0.1% formic acid in MeOH;  
gradient: 10% to 100% B over 20 minutes; flow: 1 mL min<sup>-1</sup>; detection: 225 nm.

**Existing Literature:**

- 2-(4-Fluorophenoxy)ethylamine: Beilstein Registry Number: 1941572;  
5 CAS #: 6096-89-5; Shtacher G., Taub W., *J. Med. Chem.*, 1966;9:197-203.
- 3-(4-Fluorophenyl)propylamine: Beilstein Registry Number: 7757402;  
Fujimura K., Matsumoto J., Niwa M., Kobayshi T., Kawashima Y., et al., *Bioorg. Med. Chem.*, 1997;5:1675-1684.
- 3-Phenylsulfanylpropylamine: Beilstein Registry Number: 3695289;  
10 CAS #: 34946-13-9; References to use of: Uher M., Jendrichovsky J., *Collect. Czech Chem. Commun.*, 1973;38:620-624. Tucker H., Coope J.F., *J. Med. Chem.*, 1978;21:769-773.
- 3-*p*-Tolylpropylamine: Beilstein Reference Number: 3235743; CAS #: 54930-39-1; v.Braun, Wirz, *Chem. Ber.*, 1927;60:107.
- 15 2-Methyl-3-phenylpropylamine: Beilstein Reference Number: 3237614; CAS #: 77916-78-0; Belletire J.L., Fry D.F., *Synth. Commun.*, 1988;18:29-36.
- 3-Phenyl-prop-2-ynylamine: Beilstein Reference Number: 2802264; CAS #: 78168-74-8; Tomassy B., Zwierzak A., *Synth. Commun.*, 1988;28:1201-1214.
- 20 3-(4-Fluorophenyl)-propionic acid 2,5-dioxo-pyrrolidin-1-yl ester: Beilstein Reference Number: 6657466; Shiosaki K., Lin C.W., Kopeka H.K., Craig R.A., Bruce, et al., *J. Med. Chem.*, 1992;35:2007-2014.
- 6-Bromo-5-methyl-3H-benzoxazol-2-one: Kalcheva V.B., Deligeorgiev T.G., Zaneva D.A., *Dyes and Pigments*, 1991;15:275-278.
- 25 (4-Iodophenyl)dimethylamine: CAS #: 698-70-4; Yang S.G., Kim Y.H., *Tetrahedron Lett.*, 1999;40:6051-6054.

**EXAMPLE 1**

6-[*trans*-4-(3-Phenylpropylamino)cyclohexyl]-3H-benzoxazol-2-one



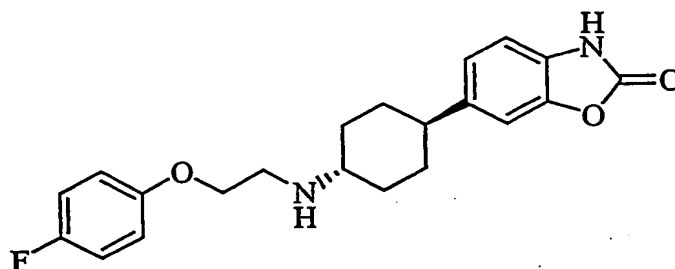
To a solution of ketone 5 (0.50 g, 2.0 mmol) in 2-propanol (30 mL) was added 3Å molecular sieves and 3-phenyl-1-propylamine 10 (0.39 g, 2.0 mmol). The reaction mixture was stirred for 4 hours. Sodium borohydride (0.11 g, 2.83 mmol) was added, and the reaction mixture was stirred overnight, quenched with MeOH, and concentrated under reduced pressure. Purification by flash chromatography (silica, 9.5:5:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH) gave 6-[*trans*-4-(3-phenylpropylamino)-cyclohexyl]-3*H*-benzoxazol-2-one (0.30 g, 42%): mp 166-170°C; IR (KBr): 2933, 1761, 1653, 1582 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 9.09 (s, 1H), 7.30-7.19 (m, 6H), 7.03 (d, *J* = 9 Hz, 1H), 6.68 (d, *J* = 9 Hz, 1H), 2.66 (m, 1H), 2.55 (t, *J* = 8 Hz, 2H), 2.37 (tt, *J* = 10, 2 Hz, 1H), 1.98 (d, *J* = 10 Hz, 1H), 1.96 (d, *J* = 10 Hz, 1H), 1.76 (d, *J* = 3 Hz, 1H), 1.56 (m, 1H), 1.45 (m, 1H), 1.39 (m, 1H), 1.18-1.05 (m, 6H); CI-MS (methane) (*m/z*): 351 [M + H]<sup>+</sup>; HRMS-API (*m/z*): [M + H]<sup>+</sup> calcd for C<sub>22</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub>, 351.2072; found, 351.2178; HPLC: method A, 7.66 minutes (96.9%); method B, 14.14 minutes (97.7%); Anal. Calcd for C<sub>22</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub>·H<sub>2</sub>O: C, 71.71; H, 7.66; N, 7.60. Found: C, 71.70; H, 7.62; N, 7.20.

The following compounds were prepared from the appropriate amines following the standard conditions. In some cases THF was used as a co-solvent to increase the solubility of the starting materials. The *trans*-isomer was usually formed as the major product. The *cis*-isomer was characterized when sufficient material was isolated.

## EXAMPLE 2

6-{*trans*-4-[2-(4-Fluorophenoxy)ethylamino]cyclohexyl}-3*H*-benzoxazol-2-one

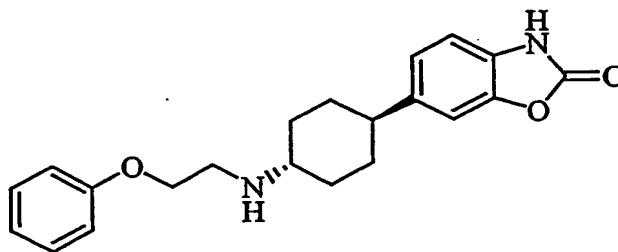
-37-



Coupling of ketone 5 and 2-(4-fluorophenoxy)ethylamine gave 6-{*trans*-4-[2-(4-fluorophenoxy)ethylamino]cyclohexyl}-3*H*-benzoxazol-2-one (0.14 g, 20%): mp 172-176°C; IR (KBr): 2931, 1759, 1654 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD): δ 7.10-6.90 (m, 7H), 4.08 (t, *J* = 5 Hz, 2H), 3.04 (t, *J* = 5 Hz, 2H), 2.62 (tt, *J* = 14, 2 Hz, 1H), 2.56 (tt, *J* = 14, 2 Hz, 1H), 2.11 (br d, *J* = 12 Hz, 2H), 1.92 (br d, *J* = 12 Hz, 2H), 1.57 (dddd, *J* = 12, 12, 12, 2 Hz, 2H), 1.33 (dddd, *J* = 12, 12, 12, 2 Hz, 2H); FAB-MS (*m/z*): 371 [M + H]<sup>+</sup>; HRMS-API (*m/z*): [M + H]<sup>+</sup> calcd for C<sub>21</sub>H<sub>23</sub>FN<sub>2</sub>O<sub>3</sub>, 371.1771; found, 371.1784; HPLC: method A, 7.51 minutes (96.4%); method B, 13.82 minutes (96.0%); Anal. Calcd for C<sub>21</sub>H<sub>23</sub>FN<sub>2</sub>O<sub>3</sub>·0.25 H<sub>2</sub>O: C, 67.27; H, 6.32; N, 7.47. Found: C, 67.09; H, 6.40; N, 7.33.

## EXAMPLE 3

6-[*trans*-4-(2-Phenoxyethylamino)cyclohexyl]-3*H*-benzoxazol-2-one



Coupling of ketone 5 and 2-phenoxyethylamine gave 6-[*trans*-4-(2-phenoxyethylamino)cyclohexyl]-3*H*-benzoxazol-2-one (0.18 g, 24%): mp 159-162°C; IR (KBr): 3262, 2926, 1759, 1654, 1600 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 7.34 (t, *J* = 2 Hz, 2H), 7.21 (s, 1H), 7.05-6.96 (m, 5H), 4.06 (t, *J* = 5 Hz, 2H), 2.98 (t, *J* = 5 Hz, 2H), 2.51 (tt, *J* = 11, 2 Hz, 1H), 2.49 (tt, *J* = 11, 2 Hz, 1H), 2.04 (br d, *J* = 11 Hz, 2H), 1.83 (br d, *J* = 11 Hz, 2H), 1.52 (dddd, *J* = 11, 11, 11, 2 Hz, 2H), 1.19 (dddd, *J* = 11, 11, 11, 2 Hz, 2H); API-MS (*m/z*):

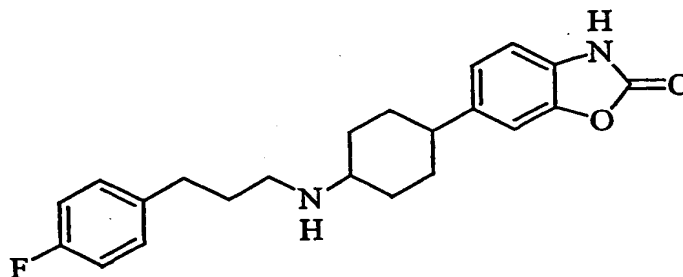
-38-

353  $[M + H]^+$ ; HRMS-API ( $m/z$ ):  $[M + H]^+$  calcd for  $C_{21}H_{24}N_2O_3$ , 353.1865; found, 353.1868; HPLC: method A, 7.39 minutes (99.5%); method B, 13.49 minutes (100%); Anal. Calcd for  $C_{21}H_{24}N_2O_3 \cdot 0.25H_2O$ : C, 70.67; H, 6.92; N, 7.85. Found: C, 70.43; H, 6.89; N, 7.49.

## EXAMPLE 4

(a) 6-{*trans*-4-[3-(4-Fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one

(b) 6-{*cis*-4-[3-(4-Fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one



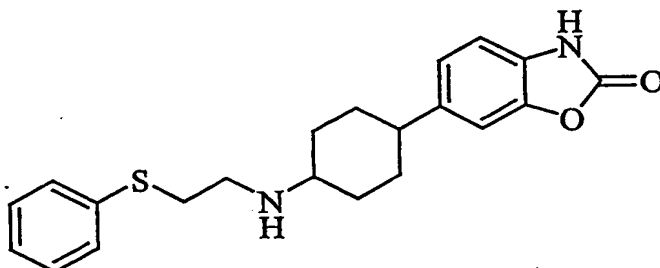
Coupling of ketone 5 and 3-(4-fluorophenyl)-1-propylamine gave (a) the *trans* isomer 6-{*trans*-4-[3-(4-fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one (HCl salt) (0.15 g, 21%): mp 293-307°C; IR (KBr): 2941, 1759  $cm^{-1}$ ;  $^1H$  NMR (500 MHz, DMSO- $d_6$ ):  $\delta$  8.83 (broad s, 1H), 7.28 (t,  $J = 6$ , 3 Hz, 1H), 7.26 (s, 1H), 7.15 (t,  $J = 6$ , 3 Hz, 2H), 7.00 (m, 4H), 3.07 (m, 1H), 2.91 (m, 2H), 2.66 (t,  $J = 2$  Hz, 2H), 2.50 (m, 1H), 2.13 (m, 2H), 1.92 (m, 2H), 1.85 (m, 3H), 1.49 (m, 4H); API-MS ( $m/z$ ): 369  $[M + H]^+$ ; HRMS-API ( $m/z$ ):  $[M + H]^+$  calcd for  $C_{22}H_{25}FN_2O_2$ , 369.1978; found, 369.1980; HPLC: method A, 7.78 minutes (99.8%); method B, 14.29 minutes (100%); Anal. Calcd for  $C_{22}H_{25}FN_2O_2 \cdot HCl \cdot 0.5H_2O$ : C, 63.84; H, 6.57; N, 6.77. Found: C, 63.64; H,

6.50; N, 6.57 and

(b) the *cis* isomer 6-{*cis*-4-[3-(4-fluorophenyl)propylamino]-cyclohexyl}-3*H*-benzoxazol-2-one (750 mg, 35%):  $^1H$  NMR (500 MHz,  $CD_3OD$ ):  $\delta$  7.27-7.22 (m, 3H), 7.13 (d,  $J = 8$  Hz, 1H), 7.05-7.10 (m, 3H), 3.43-3.39 (m, 1H), 3.08-3.04 (m, 2H), 2.85-2.80 (m, 1H), 2.76-2.72 (m, 2H), 2.08-1.81 (m, 10H).

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## EXAMPLE 5

(a) 6-[*trans*-4-(2-Phenylsulfanylethylamino)cyclohexyl]-3*H*-benzoxazol-2-one(b) 6-[*cis*-4-(2-Phenylsulfanylethylamino)cyclohexyl]-3*H*-benzoxazol-2-one

5 Coupling of ketone 5 and 2-phenylsulfanylethylamine gave (a) the *trans*-isomer 6-[*trans*-4-(2-phenylsulfanylethylamino)cyclohexyl]-3*H*-benzoxazol-2-one isolated as the HCl salt (0.13 g, 14%): mp 241-243°C; IR (KBr): 2940,

2858, 1762  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.50-7.30 (m, 5H), 7.11 (s, 1H), 7.03-6.98 (m, 2H), 3.30 (s, 4H), 3.24 (tt,  $J = 14, 2$  Hz, 1H), 2.60 (tt,  $J = 14, 2$  Hz, 1H), 2.18 (br d,  $J = 12$  Hz, 2H), 1.99 (br d,  $J = 12$  Hz, 2H), 1.57 (dddd,  $J = 12, 12, 12, 2$  Hz, 4H); API-MS ( $m/z$ ): 369  $[\text{M} + \text{H}]^+$  HRMS-API ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_2\text{S}$ , 369.1636; found, 369.1638; HPLC: method A, 7.86 minutes (98.0%); method B, 14.46 minutes (99.1%); Anal. Calcd for  $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_2\text{S} \cdot \text{HCl} \cdot 0.25 \text{H}_2\text{O}$ : C, 61.60; H, 6.28; N, 6.84. Found: C, 61.60; H,

15 6.16; N, 6.68; and

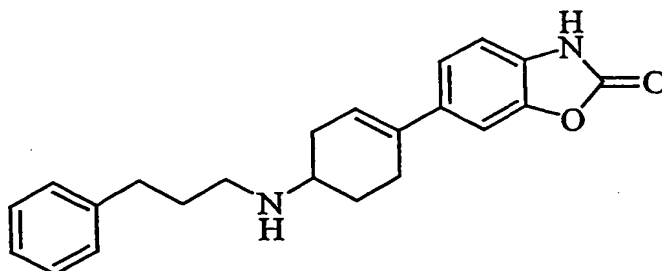
(b) The *cis*-isomer 6-[*cis*-4-(2-phenylsulfanylethylamino)-cyclohexyl]-3*H*-benzoxazol-2-one was isolated as the HCl salt (0.14 g, 9%): mp 182-190°C; IR (KBr): 2939, 1762  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.80 (br s, 2H), 7.44-6.98 (m, 8H), 3.37-3.28 (m, 4H), 3.15-3.13 (m, 1H), 2.80-2.75 (m, 1H), 1.95-1.63 (m, 8H); API-MS ( $m/z$ ): 369  $[\text{M} + \text{H}]^+$ ; HPLC: method A, 7.92 minutes (98.4%); method B, 14.47 minutes (98.2%); Anal. Calcd for  $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_2\text{S} \cdot \text{HCl} \cdot 0.50\text{H}_2\text{O}$ : C, 60.93; H, 6.33; N, 6.77. Found: C, 60.91; H, 6.37; N, 6.69.

## EXAMPLE 6

25 6-[4-(3-Phenylpropylamino)cyclohex-1-enyl]-3*H*-benzoxazol-2-one

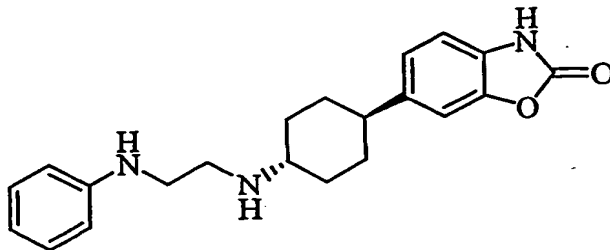


-40-



To a solution of ketone 3 (0.50 g, 2.0 mmol) in 2-propanol (30 mL) was added 3Å molecular sieves and 3-phenyl-1-propylamine (10) (0.39 g, 2.0 mmol). The reaction mixture was stirred for 4 hours. Sodium borohydride (0.11 g, 2.83 mmol) was added, and the reaction mixture was stirred overnight, quenched with MeOH, and concentrated under reduced pressure. Purification by flash chromatography (silica, 9.5:5:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH) gave 6-[4-(3-phenylpropylamino)cyclohex-1-enyl]-3H-benzoxazol-2-one (0.12 g, 21%): mp 293-295°C; IR (KBr): 2950, 1779, 1496 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 7.32 (s, 1H), 7.30-7.17 (m, 6H), 7.00 (d, *J* = 1 Hz, 1H), 6.03 (m, 1H), 2.79 (m, 1H), 2.65 (m, 4H), 2.50 (m, 4H), 1.94 (m, 2H), 1.75 (m, 2H), 1.47 (m, 2H); API-MS (*m/z*): 349 [M + H]<sup>+</sup>; HRMS-API (*m/z*): [M + H]<sup>+</sup> calcd for C<sub>22</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>, 349.1916; found, 349.1917; HPLC: method A, 7.67 minutes (97.9%); method B, 14.06 minutes (99.8%); Anal. Calcd for C<sub>22</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>·0.8H<sub>2</sub>O: C, 72.82; H, 7.11; N, 7.72. Found: C, 72.55; H, 7.13; N, 7.34.

## EXAMPLE 7

6-[*trans*-4-(2-Phenylaminoethylamino)cyclohexyl]-3H-benzoxazol-2-one

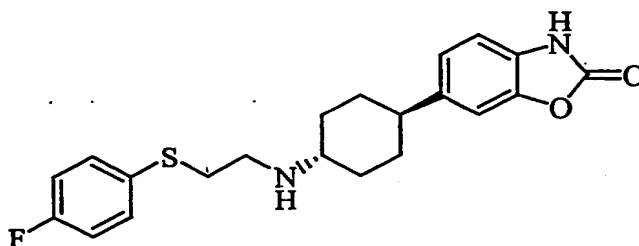
Coupling of ketone 5 and 2-(4-aminophenyl)ethylamine gave 6-[*trans*-4-(2-phenylaminoethylamino)cyclohexyl]-3H-benzoxazol-2-one (0.18 g, 26%): mp 293-295°C; IR (KBr): 2950, 1779, 1496 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 7.16 (s, 1H), 7.09 (t, *J* = 6 Hz, 2H), 7.01 (dd, *J* = 6, 1 Hz, 2H), 6.98-6.53 (m,

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3H), 5.51 (br s, 1H), 3.18 (m, 2H), 2.86 (m, 2H), 2.64 (m, 1H), 2.49 (m, 1H), 2.01 (br d,  $J = 9$  Hz, 2H), 1.81 (br d,  $J = 9$  Hz, 2H), 1.47 (dddd,  $J = 9, 9, 9, 1$  Hz, 2H), 1.24 (dddd,  $J = 9, 9, 9, 1$  Hz, 2H); API-MS ( $m/z$ ): 352 [ $M + H$ ] $^+$ ; HPLC: method A, 7.36 minutes (98.2%); method B, 13.46 minutes (98.5%); Anal. Calcd for  $C_{21}H_{25}N_3O_2$ : C, 71.77; H, 7.17; N, 11.96. Found: C, 65.64; H, 7.09; N, 10.08.

## EXAMPLE 8

6-{*trans*-4-[2-(4-Fluorophenylsulfanyl)ethylamino]cyclohexyl}-3*H*-benzoxazol-2-one

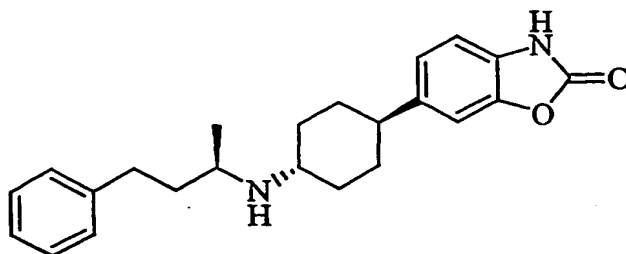


Coupling of ketone 5 and 2-(4-fluorophenylsulfanyl)ethylamine gave 6-{*trans*-4-[2-(4-fluorophenylsulfanyl)ethylamino]cyclohexyl}-3*H*-benzoxazol-2-one isolated as the HCl salt (0.10 g, 5%): mp 254-256°C; IR (KBr): 2933, 2809, 1775  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.91 (br s, 2H), 7.53-7.50 (m, 2H), 7.25-7.20 (m, 3H), 7.18-7.14 (m, 2H) 3.30-3.23 (m, 2H), 3.10-3.07 (m, 3H), 2.52-2.50 (m, 1H), 2.11-2.05 (m, 2H), 1.85-1.84 (m, 2H), 1.51-1.42 (m, 4H); API-MS ( $m/z$ ): 387 [ $M + H$ ] $^+$ ; HPLC: method A, 14.65 minutes (>99%); Anal. Calcd for  $C_{21}H_{23}FN_2O_2S \cdot \text{HCl}$ : C, 59.64; H, 5.72; N, 6.62. Found: C, 59.49; H, 5.73; N, 6.47.

## EXAMPLE 9

6-{*trans*-4-[(*R*)-1-Methyl-3-phenylpropylamino]cyclohexyl}-3*H*-benzoxazol-2-one

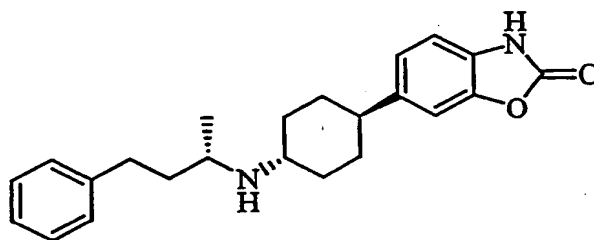
-42-



Coupling of ketone 5 and (R)-4-phenyl-2-butylamine gave 6-{*trans*-4-[(R)-1-methyl-3-phenylpropylamino]cyclohexyl}-3*H*-benzoxazol-2-one isolated as an HCl salt (0.12 g, 21%): mp 291-304°C; IR (KBr): 2945, 1752, 1623 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 8.67 (s, 1H), 7.35-7.30 (m, 5H), 7.22 (s, 1H), 6.98 (m, 2H), 3.26 (m, 4H), 2.74-2.61 (m, 2H), 2.14 (m, 2H), 1.93-1.74 (m, 3H), 1.53 (m, 4H), 1.33 (d, *J* = 6 Hz, 3H); API-MS (*m/z*): 365 [M + H]<sup>+</sup>; HPLC: method A, 8.11 minutes (97.7%); method B, 14.96 minutes (99.7%); [α]<sub>D</sub><sup>25</sup> +17.5° (c 0.08, MeOH); Anal. Calcd for C<sub>23</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>·HCl·0.5H<sub>2</sub>O: C, 67.39; H, 7.38; N, 6.83. Found: C, 67.38; H, 7.17; N, 6.71.

## EXAMPLE 10

6-{*trans*-4-[(S)-1-Methyl-3-phenylpropylamino]cyclohexyl}-3*H*-benzoxazol-2-one



Coupling of ketone 5 and (S)-4-phenyl-2-butylamine gave 6-{*trans*-4-[(S)-1-methyl-3-phenylpropylamino]cyclohexyl}-3*H*-benzoxazol-2-one (0.12 g, 21%): mp 174-176°C; IR (KBr): 2925, 1761, 1654, 1583 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 7.23-7.12 (m, 5H), 7.11 (s, 1H), 7.09 (m, 2H), 2.71 (tt, *J* = 10, 2 Hz, 1H), 2.56 (t, *J* = 5 Hz, 2H), 2.48 (tt, *J* = 10, 2 Hz, 1H), 1.87-1.70 (m, 2H), 1.63 (d, *J* = 7 Hz, 2H), 1.58 (m, 1H), 1.57-1.36 (m, 4H), 1.11-1.04 (m, 4H), 1.01 (d, *J* = 9 Hz, 3H); API-MS (*m/z*): 365 [M + H]<sup>+</sup>; HPLC:

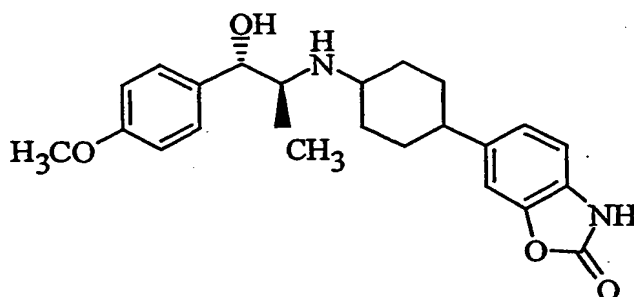
-43-

method B, 14.91 minutes (98.6%);  $[\alpha]^{25}_D -8.0^\circ$  (c 0.125, MeOH); Anal. Calcd for  $C_{23}H_{28}N_2O_2$ : C, 75.79; H, 7.74; N 7.69. Found: C, 75.48; H, 8.02; N, 7.30.

## EXAMPLE 11

(a) 6-{*trans*-4-[(1*S*,2*S*)-2-Hydroxy-2-(4-methoxyphenyl)-1-methylethylamino]-cyclohexyl}-3*H*-benzoxazol-2-one

(b) 6-{*cis*-4-[(1*S*,2*S*)-2-Hydroxy-2-(4-methoxyphenyl)-1-methylethylamino]-cyclohexyl}-3*H*-benzoxazol-2-one



Coupling of ketone 5 and  $\alpha$ -(1-aminoethyl)-4-methoxybenzyl alcohol hydrochloride 8 gave (a) the *trans*-isomer 6-{*trans*-4-[(1*S*,2*S*)-2-hydroxy-2-(4-methoxyphenyl)-1-methylethylamino]cyclohexyl}-3*H*-benzoxazol-2-one isolated the HCl salt (0.18 g, 12%): mp 241-249°C; IR (KBr): 3300, 2943, 1758  $cm^{-1}$ ;  $^1H$  NMR (500 MHz, DMSO- $d_6$ ):  $\delta$  8.52 (br s, 2H), 7.33 (d,  $J = 9$  Hz, 2H), 7.19 (s, 1H), 7.14-7.00 (m, 2H), 6.95 (d,  $J = 9$  Hz, 2H), 6.05 (br s, 1H), 5.09 (br s, 1H), 3.76 (s, 3H), 3.47 (br s, 1H), 3.23-3.20 (m, 1H), 2.60-2.46 (m, 1H), 2.31-2.08 (m, 2H), 1.91-1.87 (m, 2H), 1.65-1.50 (m, 4H), 0.97 (d,  $J = 7$  Hz, 3H); CI-MS (methane) ( $m/z$ ): 397  $[M + H]^+$ ; HRMS-API ( $m/z$ ):  $[M + H]^+$  calcd for  $C_{23}H_{28}N_2O_4$ , 397.2127; found, 397.2126; HPLC: method A, 6.69 minutes (97.8%); method B, 11.90 minutes (99.3%); Anal. Calcd for  $C_{23}H_{28}N_2O_4 \cdot HCl \cdot 0.50H_2O$ : C, 62.51; H, 6.84; N, 6.34. Found: C, 62.63; H, 6.78; N, 6.25; and

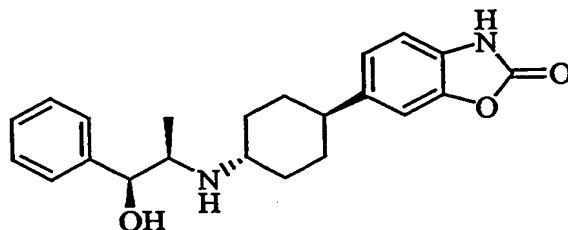
(b) the *cis*-isomer 6-{*cis*-4-[(1*S*,2*S*)-2-hydroxy-2-(4-methoxyphenyl)-1-methylethylamino]cyclohexyl}-3*H*-benzoxazol-2-one was isolated as the HCl salt (0.068 g, 4%): mp 195-197°C; IR (KBr): 2940, 1758  $cm^{-1}$ ;  $^1H$  NMR (500 MHz, DMSO- $d_6$ ):  $\delta$  8.40-8.25 (m, 2H), 7.37-7.32 (m, 3H), 7.13 (br d,  $J = 8$  Hz, 1H),

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7.03 (d,  $J = 8$  Hz, 1H), 6.94 (d,  $J = 9$  Hz, 2H), 6.05-6.03 (m, 1H), 5.16-5.15 (m, 1H), 3.75 (s, 3H), 3.56-3.41 (m, 2H), 2.73-2.79 (m, 1H), 2.12-1.78 (m, 6H), 1.73-1.65 (m, 2H), 0.99 (d,  $J = 7$  Hz, 3H); CI-MS (methane) ( $m/z$ ): 397  $[M + H]^+$ ; HRMS-API ( $m/z$ ):  $[M + H]^+$  calcd for  $C_{23}H_{28}N_2O_4$ , 397.2127; found, 397.2125; HPLC: method A, 7.04 minutes (96.4%); method B; 12.44 minutes (96.8%); Anal. Calcd for  $C_{23}H_{28}N_2O_4 \cdot HCl \cdot 0.25H_2O$ : C, 63.15; H, 6.80; N, 6.40. Found: C, 63.02; H, 6.69; N, 6.29.

## EXAMPLE 12

6-{*trans*-4-[(1*S*,2*R*)-2-Hydroxy-1-methyl-2-phenylethylamino]cyclohexyl}-3*H*-benzoxazol-2-one



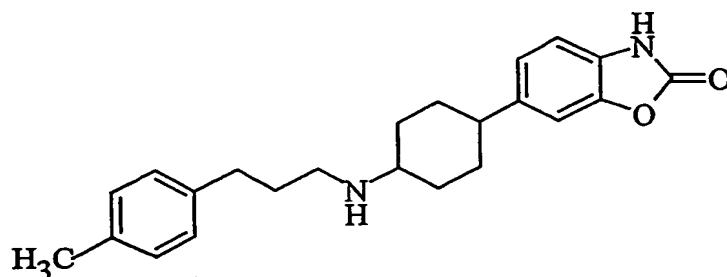
Coupling of ketone 5 and (1*S*,2*R*)-(+)-norephedrine hydrochloride gave the *trans*-isomer 6-{*trans*-4-[(1*S*,2*R*)-2-hydroxy-1-methyl-2-phenylethylamino]cyclohexyl}-3*H*-benzoxazol-2-one isolated as the HCl salt (0.12 g, 21%); mp 251-256°C; IR (KBr): 2942, 1754, 1624  $cm^{-1}$ ;  $^1H$  NMR (300 MHz, DMSO- $d_6$ ):  $\delta$  8.59 (s, 2H), 7.44-7.30 (m, 5H), 7.20 (s, 1H), 7.02-6.98 (m, 2H), 6.17 (d,  $J = 4$  Hz, 1H), 5.15 (m, 1H), 3.52 (m, 1H), 2.58 (m, 1H), 2.47 (m, 1H), 2.37 (m, 1H), 1.88 (m, 2H), 1.62 (m, 4H), 0.97 (d,  $J = 6$  Hz, 3H); API-MS ( $m/z$ ): 367  $[M + H]^+$ ; HPLC: method A, 7.59 minutes (97.9%); method B, 14.18 minutes (98.5%); Anal. Calcd for  $C_{22}H_{26}N_2O_3 \cdot HCl$ : C, 62.77; H, 6.94; N, 6.66. Found: C, 62.59; H, 6.64; N, 6.39.

## EXAMPLE 13

(a) 6-[*cis*-4-(3-*p*-Tolylpropylamino)cyclohexyl]-3*H*-benzoxazol-2-one

(b) 6-[*trans*-4-(3-*p*-Tolylpropylamino)cyclohexyl]-3*H*-benzoxazol-2-one

-45-

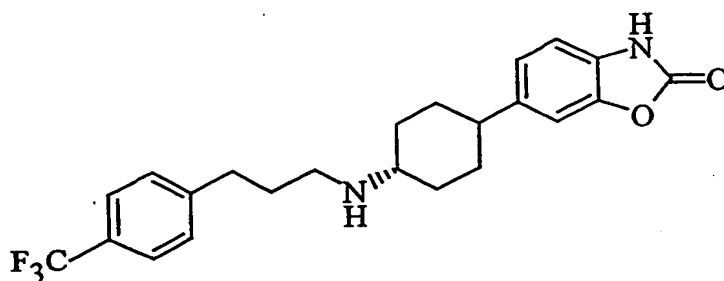


Coupling of ketone 5 and 3-*p*-tolylpropylamine gave (a) the *cis*-isomer 6-[*cis*-4-(3-*p*-tolylpropylamino)cyclohexyl]-3*H*-benzoxazol-2-one isolated as the HCl salt (0.12 g, 7%): mp 263-265°C; IR (KBr): 2941, 1765 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 8.64 (br s, 2H), 7.36-7.35 (m, 1H), 7.12-6.99 (m, 6H), 3.33-3.29 (m, 1H), 2.90-2.96 (m, 2H), 2.66-2.60 (m, 3H), 2.27 (s, 3H), 2.01-1.89 (m, 6H), 1.77-1.69 (m, 2H), 1.65-1.59 (m, 2H); CI MS (methane) (*m/z*): 365 [M + H]<sup>+</sup>; HRMS-API (*m/z*): [M + H]<sup>+</sup> calcd for C<sub>23</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>, 365.2229; found, 365.2228; HPLC: method A, 7.14 minutes (95.2%); method B, 13.08 minutes (96.6%); Anal. Calcd for C<sub>23</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>·HCl·0.50H<sub>2</sub>O: C, 68.13; H, 7.33; N, 6.91. Found: C, 68.33; H, 7.27; N, 6.92; and (b) the *trans*-isomer 6-[*trans*-4-(3-*p*-tolylpropylamino)cyclohexyl]-3*H*-benzoxazol-2-one was isolated as the HCl salt (0.27 g, 16%): mp 295-301°C; IR (KBr): 2942, 1763 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 8.79 (m, 2H), 7.17 (br s, 1H), 7.13-7.11 (m, 4H), 7.02-6.97 (m, 2H) 3.05 (br s, 1H), 2.92-2.89 (m, 2H), 2.63 (t, *J* = 8 Hz, 2H), 2.53-2.50 (m, 1H), 2.27 (s, 3H), 2.16-2.10 (m, 2H), 1.95-1.85 (m, 4H), 1.55-1.46 (m, 4H); CI-MS (methane) (*m/z*): 365 [M + H]<sup>+</sup>; HPLC: method A, 7.02 minutes (96.5%); method B, 13.11 minutes (98.8%); Anal. Calcd for C<sub>23</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>·HCl: C, 68.90; H, 7.29; N, 6.99. Found: C, 68.78; H, 7.21; N 6.87.

## EXAMPLE 14

6-{*trans*-4-[3-(4-Trifluoromethylphenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one

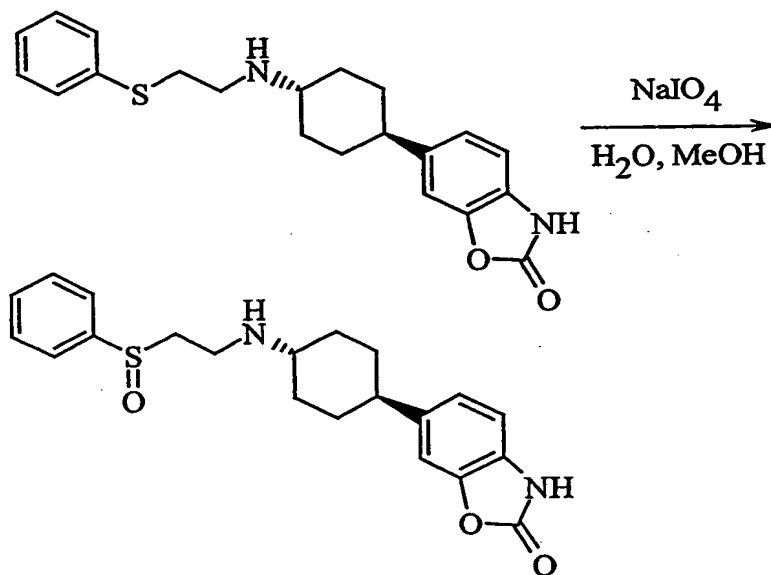
-46-



Coupling of ketone 5 and 3-(4-trifluoromethylphenyl)-1-propylamine gave 6-{*trans*-4-[3-(4-trifluoromethylphenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one isolated as an HCl salt (0.78 g, 33%): mp 285-295°C; IR (KBr): 2945, 1766 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 11.47 (s, 1H), 8.81 (s, 2H), 7.68 (d, *J* = 8 Hz, 2H), 7.49 (d, *J* = 8 Hz, 2H), 7.17 (s, 1H), 7.20-6.97 (m, 2H), 3.10-3.02 (m, 1H), 2.98-2.91 (m, 2H), 2.80 (t, *J* = 8 Hz, 2H), 2.57-2.50 (m, 1H), 2.18-2.11 (m, 2H), 2.01-1.95 (m, 2H), 1.90-1.84 (m, 2H), 1.51 (m, 4H); CI-MS (*m/z*): 419 [M + H]<sup>+</sup>; HPLC: method A, 6.87 minutes (97.7%); Anal. Calcd for C<sub>23</sub>H<sub>25</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>·HCl: C, 60.73; H, 5.76; N, 6.16. Found: C, 60.63; H, 5.97; N, 6.04.

## EXAMPLE 15

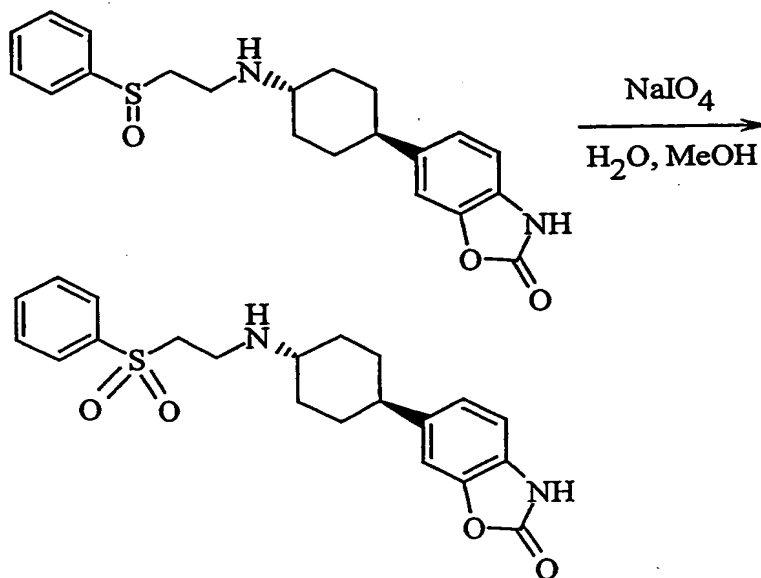
6-[*trans*-4-(2-Benzenesulfinylethylamino)cyclohexyl]-3*H*-benzoxazol-2-one



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To a stirred, ice-cold, suspension of  $\text{NaIO}_4$  (0.13 g, 0.62 mmol) in  $\text{H}_2\text{O}$  (1.2 mL) was added 6-[*trans*-4-(2-phenylsulfonyl-ethylamino)cyclohexyl]-3*H*-benzoxazol-2-one (0.25 g, 0.62 mmol). The viscous reaction mixture was diluted with  $\text{H}_2\text{O}$  (1.5 mL), warmed to room temperature, and then further diluted with MeOH (15 mL). After 21 hours, the reaction mixture was concentrated under reduced pressure. Purification by flash chromatography (silica, 89:10:1  $\text{CH}_2\text{Cl}_2$ :MeOH: $\text{NH}_4\text{OH}$ ) gave the free base of 6-[*trans*-4-(2-benzenesulfinylethylamino)cyclohexyl]-3*H*-benzoxazol-2-one, which was converted to the HCl salt (0.13 g, 49%): mp 107-110°C; IR (KBr): 2936, 2783, 1768,  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  9.03 (br s, 2H), 7.74-7.60 (m, 5H), 7.16 (s, 1H), 6.99-6.97 (m, 2H), 3.48-3.43 (m, 1H), 3.33-3.29 (m, 1H), 3.18-3.04 (m, 4H), 2.54-2.52 (m, 2H), 1.86-1.84 (m, 2H), 1.51-1.44 (m, 4H); API-MS ( $m/z$ ): 385  $[\text{M} + \text{H}]^+$ ; HPLC: method A, 7.01 minutes (98.1%); method B, 12.83 minutes (99.2%); Anal. Calcd for  $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_3\text{S}\cdot\text{HCl}\cdot 1.25 \text{ H}_2\text{O}$ : C, 56.88; H, 6.25; N, 6.32. Found: C, 56.86; H, 6.18; N, 6.22.

## EXAMPLE 16

6-[*trans*-4-(2-Benzenesulfonyl-ethylamino)cyclohexyl]-3*H*-benzoxazol-2-one



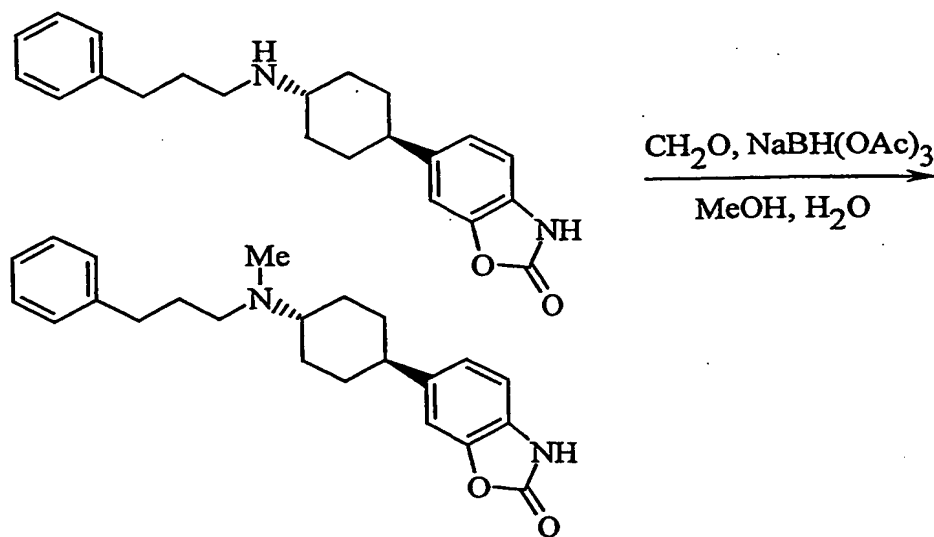
-48-

To a stirred suspension of NaIO<sub>4</sub> (0.30 g, 1.4 mmol) in a mixture of H<sub>2</sub>O (5 mL) and MeOH (5 mL) was added 6-[*trans*-4-(2-phenylsulfanylethylamino)-cyclohexyl]-3*H*-benzoxazol-2-one (0.19 g, 0.47 mmol). After 48 hours, a second portion of NaIO<sub>4</sub> (0.20 g, 0.93 mmol) was added, and stirring was continued overnight. The reaction mixture was heated at 60°C for 6 hours, then cooled to room temperature and concentrated under reduced pressure. The solids were suspended in a 2:1 mixture of MeOH and CH<sub>2</sub>Cl<sub>2</sub> and the solution filtered. The filtrate was concentrated under reduced pressure. Purification by flash chromatography (silica, 50:49:1 acetone:CH<sub>2</sub>Cl<sub>2</sub>:MeOH) gave the free base 6-[*trans*-4-(2-benzenesulfonylethylamino)cyclohexyl]-3*H*-benzoxazol-2-one, which was converted to the HCl salt (0.050 g, 24%): mp 202-208°C; IR (KBr): 3448, 2939, 1763 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 8.97 (br s, 2H), 7.98-7.71 (m, 5H), 7.16 (s, 1H), 6.99-6.98 (m, 2H), 3.77-3.74 (m, 1H), 3.25-3.23 (m, 1H), 3.21-3.20 (m, 4H), 2.09-2.04 (m, 2H), 1.90-1.40 (m, 2H), 1.52-1.40 (m, 4H); CI-MS (methane) (*m/z*): 401 [M + H]<sup>+</sup>; HRMS-API (*m/z*): [M + H]<sup>+</sup> calcd for C<sub>21</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>S, 401.1535; found, 401.1535; HPLC: method A, 6.34 minutes (97.3%); method B, 11.06 minutes (99.1%); Anal. Calcd for C<sub>21</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>S·HCl·0.50H<sub>2</sub>O: C, 56.56; H, 5.88; N, 6.28. Found: C, 56.29; H, 5.65; N, 6.13.

## EXAMPLE 17

6-{*trans*-4-[Methyl(3-phenylpropyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one

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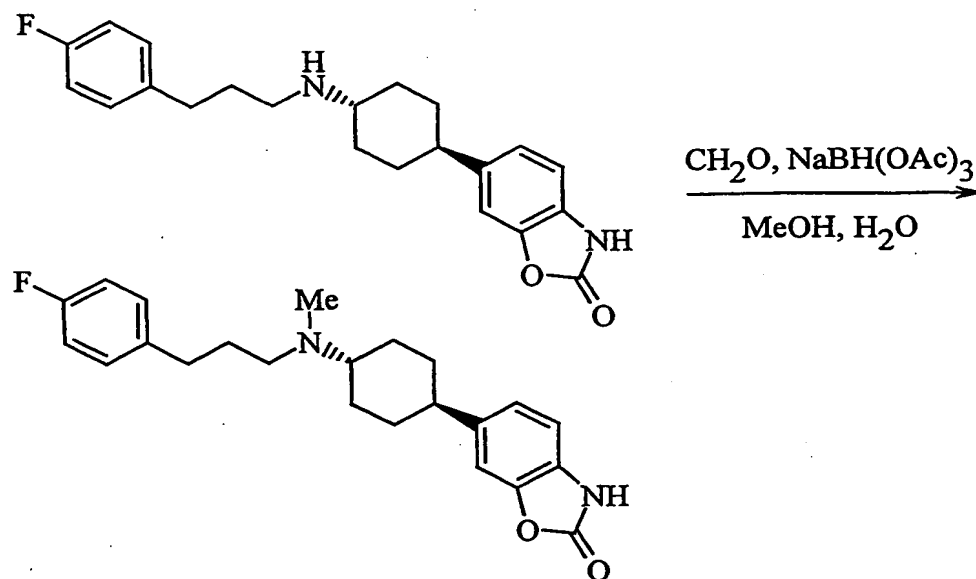


To a stirred solution of 6-[*trans*-4-(3-phenylpropylamino)cyclohexyl]-3*H*-benzoxazol-2-one (263 mg, 0.750 mmol) in MeOH (10 mL) was added H<sub>2</sub>O (0.5 mL) and *p*-formaldehyde (113 mg, 3.75 mmol). After stirring the reaction mixture for 3 hours, NaBH(OAc)<sub>3</sub> was added, and stirring was continued for 12 hours. Solid NaOH was added to give a clear solution, which was then concentrated under reduced pressure. Purification by flash chromatography (silica, 95:4:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH) gave 6-{*trans*-4-[methyl(3-phenylpropyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one (160 mg, 59%), as a white solid: mp 58-62°C; IR (KBr): 2929, 1774 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 8.97 (br s, 1H), 7.26-7.12 (m, 6H), 6.99-6.98 (m, 2H), 2.63 (m, 2H), 2.57 (t, *J* = 7 Hz, 2H), 2.56 (m, 1H), 2.38 (m, 2H), 2.18 (s, 3H), 1.78 (m, 2H), 1.68 (m, 2H), 1.37 (m, 2H), 1.27 (m, 2H); CI-MS (methane) (*m/z*): 365 [M + H]<sup>+</sup>; HRMS-API (*m/z*): [M + H]<sup>+</sup> calcd for C<sub>23</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>, 365.2229; found, 365.2231; HPLC: method A, 5.95 minutes (95.3%); method B, 10.12 minutes (97.6%); Anal. Calcd for C<sub>23</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>·0.25H<sub>2</sub>O: C, 74.87; H, 7.79; N, 7.59. Found: C, 74.77; H, 7.71; N, 7.81.

## EXAMPLE 18

6-(*trans*-4-{[3-(4-Fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one

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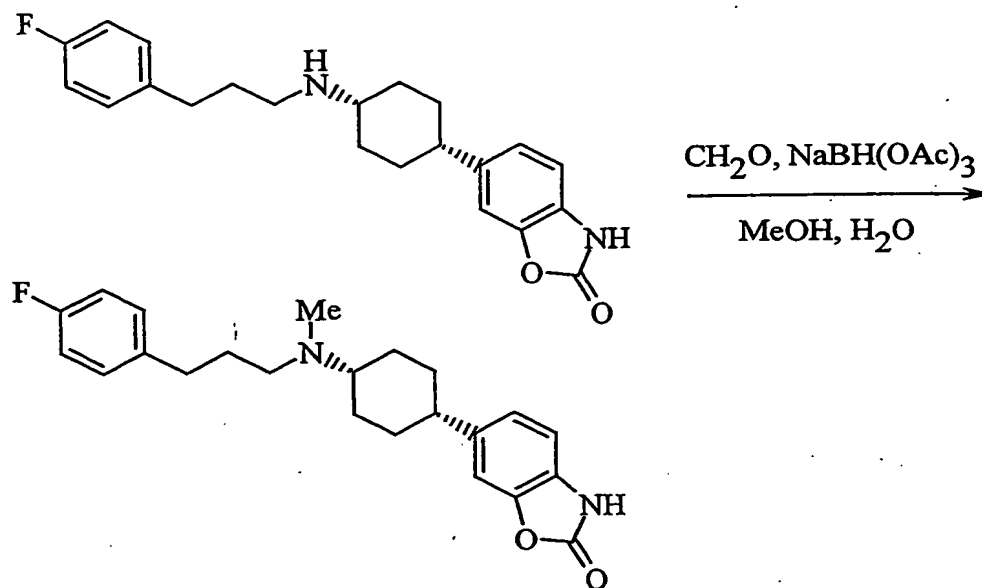


Coupling of 6-{*trans*-4-[3-(4-fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one (519 mg, 1.40 mmol) and *p*-formaldehyde (210 mg, 1.00 mmol), following the procedure described in Example 17, gave 6-{*trans*-4-  
 5 { [3-(4-fluorophenyl)propyl]methylamino } cyclohexyl }-3*H*-benzoxazol-2-one (135 mg, 26%), as a white solid: mp 62-65°C; IR (KBr): 2930, 1774, 1654, 1509 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 7.24-6.94 (m, 8H), 2.57 (m, 3H), 2.39 (m, 1H), 2.36 (m, 4H), 2.18 (s, 3H), 1.82 (m, 2H), 1.77 (m, 2H), 1.44 (m, 2H), 1.35 (m, 2H); CI-MS (methane) (*m/z*): 383 [M + H]<sup>+</sup> HRMS-API (*m/z*):  
 10 [M + H]<sup>+</sup>; calcd for C<sub>23</sub>H<sub>27</sub>FN<sub>2</sub>O<sub>2</sub>, 383.2135; found, 383.2133; HPLC: method A, 6.04 minutes (95.7%); method B, 10.73 minutes (96.8%); Anal. Calcd for C<sub>23</sub>H<sub>27</sub>FN<sub>2</sub>O<sub>2</sub>·0.75H<sub>2</sub>O: C, 69.76; H, 7.25; N, 7.07. Found: C, 69.53; H, 6.97; N, 7.23.

## EXAMPLE 19

15 6-{*cis*-4-{ [3-(4-Fluorophenyl)propyl]methylamino } cyclohexyl }-3*H*-benzoxazol-2-one

-51-

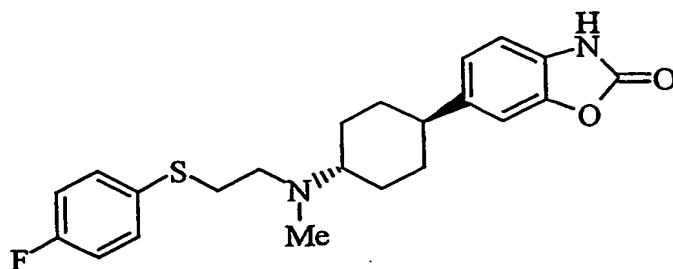


Coupling of 6-*cis*-4-[3-(4-fluorophenyl)propylamino]-cyclohexyl}-3*H*-benzoxazol-2-one (519 mg, 1.40 mmol) and *p*-formaldehyde (210 mg, 1.00 mmol), following the procedure described in Example 17, gave 6-(*cis*-4-[[3-(4-fluorophenyl)propyl]methylamino]cyclohexyl)-3*H*-benzoxazol-2-one (600 mg, 78%), as an off-white glass: IR (KBr): 2944, 1770  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ ):  $\delta$  11.50 (s, 1H), 10.05 (s, 1H), 7.41 (s, 1H), 7.31-7.26 (m, 2H), 7.16-7.09 (m, 3H), 6.99 (d,  $J = 8$  Hz, 1H), 3.38-3.30 (m, 1H), 3.15-3.07 (m, 1H), 3.07-2.98 (m, 1H), 2.81-2.77 (m, 1H), 2.70 (d,  $J = 5$  Hz, 3H), 2.65-2.49 (m, 2H), 2.13-1.66 (m, 10H); ESI-MS ( $m/z$ ): 383  $[\text{M} + \text{H}]^+$ ; HRMS-API ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{23}\text{H}_{27}\text{FN}_2\text{O}_2$ , 383.2135; found, 383.2132; HPLC: method A, 5.88 minutes (98.7%); method B, 10.97 minutes (98.6%); Anal. Calcd for  $\text{C}_{23}\text{H}_{27}\text{FN}_2\text{O}_2 \cdot \text{HCl} \cdot 0.25\text{H}_2\text{O}$ : C, 65.24; H, 6.78; N, 6.62. Found: C, 65.41; H, 6.97; N, 6.72.

## EXAMPLE 20

6-{*trans*-4-[2-(4-Fluorophenyl)sulfanylethyl]methylamino]cyclohexyl}-3*H*-benzoxazol-2-one

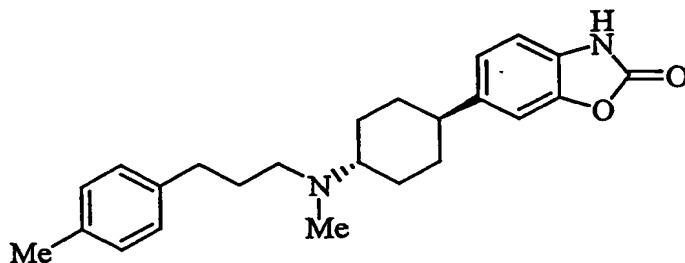
-52-



6-{*trans*-4-[2-(4-Fluorophenylsulfanyl)ethylamino]cyclohexyl}-3*H*-benzoxazol-2-one (197 mg, 0.51 mmol) was coupled with *p*-formaldehyde (76 mg, 2.5 mmol), following the procedure described in Example 17, except CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added. Formation of the HCl salt gave 6-{*trans*-4-[2-(4-fluorophenylsulfanylethyl)methylamino]cyclohexyl}-3*H*-benzoxazol-2-one (154 mg, 69%), as a white solid: mp 213-217°C; IR (KBr): 2942, 1770, 1492 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 11.49 (s, 1H), 10.64 (br s, 1H), 7.56-7.51 (m, 2H), 7.25-7.21 (m, 2H), 7.14 (s, 1H), 7.00 (br s, 2H), 3.50-3.31 (m, 3H), 3.31-3.15 (m, 2H), 2.72 (d, *J* = 5 Hz, 3H), 2.54-2.50 (m, 1H), 2.14-2.02 (m, 2H), 1.90-1.85 (m, 2H), 1.68-1.49 (m, 4H); CI-MS (methane) (*m/z*): 401 [M + H]<sup>+</sup>; HPLC: method A, 5.95 minutes (98.1%); Anal. Calcd for C<sub>22</sub>H<sub>25</sub>FN<sub>2</sub>O<sub>2</sub>S·HCl: C, 60.47; H, 6.00; N, 6.41. Found: C, 60.17; H, 6.00; N, 7.34.

## EXAMPLE 21

6-{*trans*-4-[Methyl-3-(*p*-Tolylpropyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one



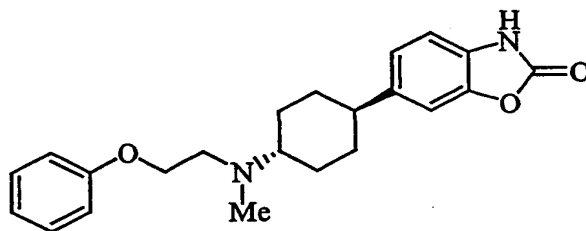
6-[*trans*-4-(3-*p*-Tolylpropylamino)cyclohexyl]-3*H*-benzoxazol-2-one (300 mg, 0.82 mmol) was coupled with *p*-formaldehyde (120 mg, 4.1 mmol) following the procedure described in Example 17 except CH<sub>2</sub>Cl<sub>2</sub> (8 mL) was added. Also, additional NaBH(OAc)<sub>3</sub> and *p*-formaldehyde were added at intervals to drive the reaction to completion. Formation of the HCl salt gave 6-{*trans*-4-

-53-

[methyl-3-(*p*-tolylpropyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one (224 mg, 66%), as a white solid: mp 213-225°C; IR (KBr): 2944, 1771, 1498, 1451 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 11.48 (s, 1H), 9.85 (br s, 1H), 7.16-7.10 (m, 5H), 7.00 (br s, 2H), 3.32-3.26 (m, 1H), 3.19-3.11 (m, 1H), 3.04-2.97 (m, 1H), 2.70 (d, *J* = 4 Hz, 3H), 2.65-2.50 (m, 3H), 2.28 (s, 3H), 2.12-2.02 (m, 2H), 2.02-1.94 (m, 2H), 1.94-1.88 (m, 2H), 1.68-1.50 (m, 4H); CI-MS (methane) (*m/z*): 379 [M + H]<sup>+</sup>; calcd for C<sub>24</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>, 379.2385; found, 379.2397; HPLC: method A, 6.45 minutes (99.4%); method B, 15.17 minutes (>99%); Anal. Calcd for C<sub>24</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>·HCl·0.5H<sub>2</sub>O: C, 67.99; H, 7.61; N, 6.61. Found: C, 67.96; H, 7.57; N, 6.84.

## EXAMPLE 22

6-{*trans*-4-[Methyl(2-phenoxyethyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one



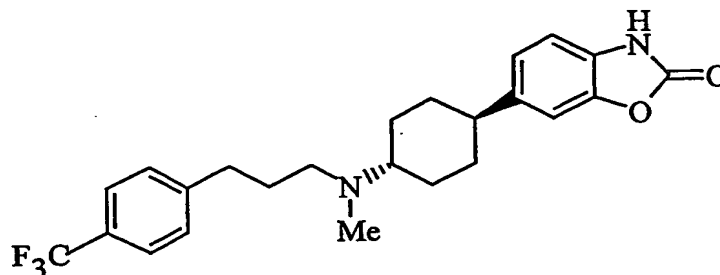
6-*trans*-[4-(2-Phenoxyethylamino)cyclohexyl]-3*H*-benzoxazol-2-one (250 mg, 0.71 mmol) was coupled with *p*-formaldehyde (100 mg, 3.5 mmol) following the procedure described in Example 17, except CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added. Also, additional NaBH(OAc)<sub>3</sub> and NaBH<sub>4</sub> were added at intervals to drive the reaction to completion. Formation of the HCl salt gave 6-{*trans*-4-[methyl(2-phenoxyethyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one (219 mg, 77%), as a white solid: mp 277-285°C; IR (KBr): 2939, 1769, 1496 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 11.48 (s, 1H), 10.00 (br s, 1H), 7.37-7.32 (m, 2H), 7.17 (s, 1H), 7.03-6.99 (m, 5H), 4.43-4.38 (m, 2H), 3.69-3.61 (m, 1H), 3.50-3.37 (m, 2H), 2.84 (d, *J* = 4 Hz, 3H), 2.61-2.52 (m, 1H), 2.22-2.12 (m, 2H), 1.99-1.91 (m, 2H), 1.72-1.50 (m, 4H); CI-MS (methane) (*m/z*): 367 [M + H]<sup>+</sup>; calcd for C<sub>22</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub>, 367.2021; found, 367.2018; HPLC: method A, 5.48 minutes (97.2%); method B, 12.81 minutes (98.0%); Anal. Calcd for

-54-

$C_{22}H_{26}N_2O_3 \cdot HCl \cdot 0.1NH_4Cl$ : C, 64.72; H, 6.76; N, 7.20. Found: C, 64.52; H, 6.86; N, 7.34.

## EXAMPLE 23

6-{*trans*-4-[Methyl-3-(4-Trifluoromethylphenyl)propylamino]cyclohexyl}-3*H*-  
5 benzoxazol-2-one



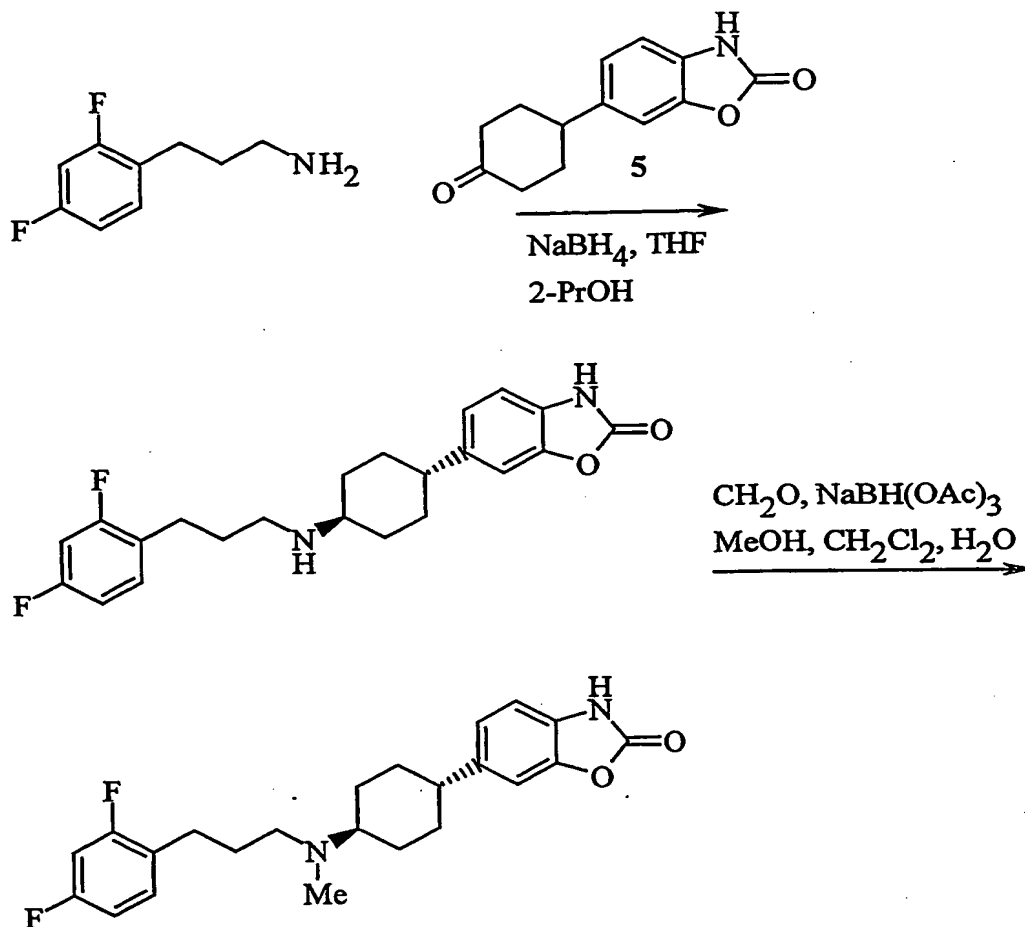
6-{*trans*-4-[3-(4-Trifluoromethylphenyl)propylamino]cyclohexyl}-3*H*-  
benzoxazol-2-one (200 mg, 0.48 mmol) was coupled with *p*-formaldehyde  
(72 mg, 2.4 mmol) following the procedure described in Example 17, except  
10  $CH_2Cl_2$  (5 mL) was added. Also, additional  $NaBH(OAc)_3$  was added at intervals  
to drive the reaction to completion. Formation of the HCl salt gave 6-{*trans*-4-  
[methyl-3-(4-trifluoromethylphenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-  
one (175 mg, 77%), as a white solid: mp 227-234°C; IR (KBr): 2945, 1771,  
1497  $cm^{-1}$ ;  $^1H$  NMR (500 MHz,  $DMSO-d_6$ ):  $\delta$  11.48 (s, 1H), 10.00 (br s, 1H),  
15 7.68 (d,  $J = 8$  Hz, 2H), 7.50 (d,  $J = 8$  Hz, 2H), 7.16 (s, 1H), 6.99 (s, 2H), 3.33-  
3.29 (m, 1H), 3.22-3.14 (m, 1H), 3.08-3.00 (m, 1H), 2.81-2.72 (m, 2H), 2.71 (d,  
 $J = 5$  Hz, 3H), 2.59-2.51 (m, 1H), 2.15-2.05 (m, 4H), 1.94-1.88 (m, 2H), 1.68-  
1.51 (m, 4H); CI-MS (methane) ( $m/z$ ): 433  $[M + H]^+$ ; calcd for  $C_{24}H_{27}F_3N_2O_2$ ,  
433.2103; found, 433.2105; HPLC: method C, 14.09 minutes (95.8%); method D,  
20 15.99 minutes (97.3%); Anal. Calcd for  $C_{24}H_{27}F_3N_2O_2 \cdot HCl \cdot H_2O$ : C, 59.20; H,  
6.21; N, 5.75. Found: C, 59.22; H, 6.22; N, 5.55.

## EXAMPLE 24

(a) 6-{*trans*-4-[3-(2,4-Difluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-  
2-one

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(b) 6-(*trans*-4-{[3-(2,4-Difluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one



- Coupling of ketone 5 and 3-(2,4-difluorophenyl)-1-propylamine, using the method given in Example 1, gave (a) 6-{*trans*-4-[3-(2,4-difluorophenyl)-propylamino]-cyclohexyl}-3*H*-benzoxazol-2-one and (0.75 g, 37%), isolated as the HCl salt:  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ ):  $\delta$  11.49 (s, 1H), 8.84 (br s, 2H), 7.40 (ddd,  $J = 9, 9, 7$  Hz, 1H), 7.22-7.18 (m, 2H), 7.05 (ddd,  $J = 8, 8, 2$  Hz, 1H), 7.01 (dd,  $J = 8, 1$  Hz, 1H), 6.99 (d,  $J = 8$  Hz, 1H), 3.11-3.02 (m, 1H), 2.98-2.92 (m, 2H), 2.70 (t,  $J = 8$  Hz, 2H), 2.56-2.49 (m, 1H), 2.18-2.11 (m, 2H), 1.96-1.86 (m, 4H), 1.51 (m, 4H), and
- (b) 6-{*trans*-4-[3-(2,4-Difluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one and (435 mg, 1.0 mmol) was coupled with *p*-formaldehyde (150 mg, 5.1 mmol) following the procedure described in Example 17, except  $\text{CH}_2\text{Cl}_2$  (15 mL) was added. Also, additional  $\text{NaBH}(\text{OAc})_3$  was added at

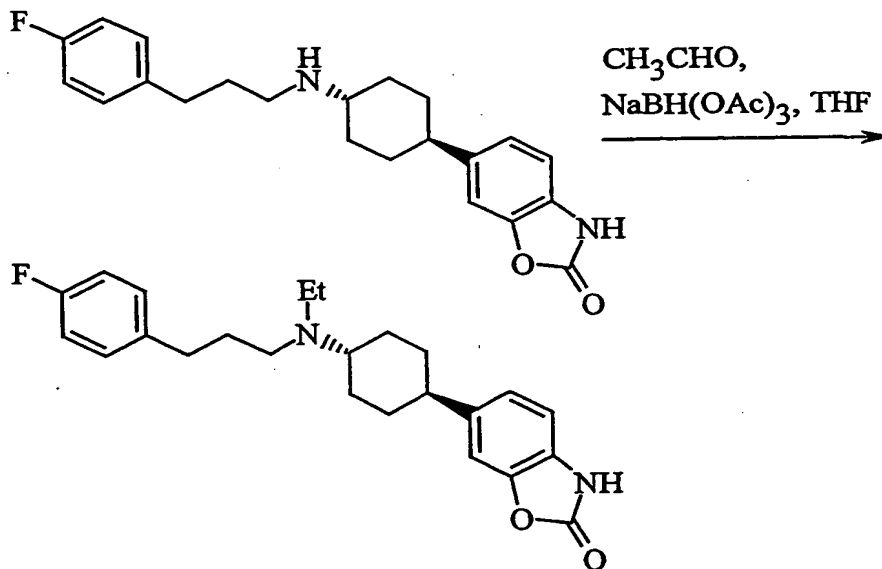


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intervals to drive the reaction to completion. Formation of the HCl salt gave (b) 6-(*trans*-4-{{3-(2,4-difluorophenyl)propyl}methylamino}cyclohexyl)-3*H*-benzoxazol-2-one (314 mg, 72%), as a white solid: mp 269-272°C; IR (KBr): 2947, 1768  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  11.50 (s, 1H), 10.37 (br s, 1H), 7.41 (ddd,  $J = 8, 8, 7$  Hz, 1H), 7.22-7.16 (m, 2H), 7.07-7.04 (m, 1H), 7.00 (s, 2H), 3.32-3.28 (m, 1H), 3.20-3.12 (m, 1H), 3.08-2.99 (m, 1H), 2.72-2.61 (m, 5H), 2.59-2.50 (m, 1H), 2.15-2.07 (m, 2H), 2.04-1.96 (m, 2H), 1.90-1.89 (m, 2H), 1.67-1.51 (m, 4H); ESI-MS ( $m/z$ ): 401  $[\text{M} + \text{H}]^+$ ; HPLC: method A, 5.96 minutes (>99%); Anal. Calcd for  $\text{C}_{23}\text{H}_{26}\text{F}_2\text{N}_2\text{O}_2 \cdot \text{HCl}$ : C, 63.23; H, 6.23; N, 6.41. Found: C, 63.03; H, 6.16; N, 6.25.

## EXAMPLE 25

6-(*trans*-4-{{Ethyl-[3-(4-fluorophenyl)propyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one



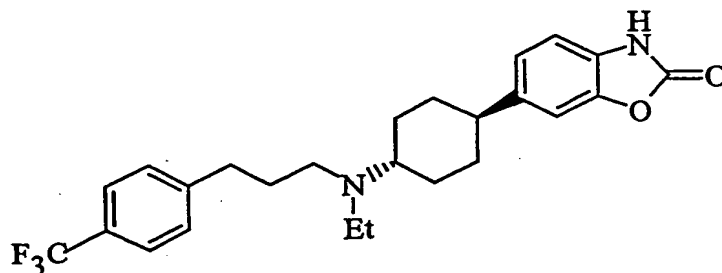
To a stirred solution of 6-{{*trans*-4-[3-(4-fluorophenyl)-propylamino]-cyclohexyl}-3*H*-benzoxazol-2-one (1.0 g, 2.7 mmol) in THF (60 mL) was added acetaldehyde (240 mg, 5.4 mmol) and 3Å molecular sieves. After stirring the reaction mixture for 5 to 10 minutes,  $\text{NaBH}(\text{OAc})_3$  (0.81 mg, 3.8 mmol) was added, and stirring was continued for 0.5 hours. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in MeOH.

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The solution was brought to pH = 10 with 2N NaOH, filtered through Celite, and concentrated under reduced pressure. Purification by flash chromatography (silica, 89:10:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH), followed by formation of the HCl salt gave 6-(*trans*-4-{[ethyl-[3-(4-fluorophenyl)propyl]amino}-cyclohexyl)-3*H*-benzoxazol-2-one (395 mg, 33%), as a white solid: mp 228-231°C; IR (KBr): 2946, 1769, 1509 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 11.47 (s, 1H), 9.65 (br s, 1H), 7.33-7.29 (m, 2H), 7.17-7.12 (m, 3H), 7.00 (s, 2H), 3.39-3.32 (m, 1H), 3.24-3.08 (m, 3H), 3.05-2.98 (m, 1H), 2.68 (q, *J* = 7, 3 Hz, 2H), 2.60-2.50 (m, 1H), 2.14-2.09 (m, 2H), 2.04-1.98 (m, 2H), 1.93-1.87 (m, 2H), 1.69-1.55 (m, 4H), 1.26 (t, *J* = 7 Hz, 3H); CI-MS (methane) (*m/z*): 397 [M + H]<sup>+</sup>; HPLC: method A, 6.37 minutes (97.7%); Anal. Calcd for C<sub>24</sub>H<sub>29</sub>FN<sub>2</sub>O<sub>2</sub>·HCl: C, 66.58; H, 6.98; N, 6.47. Found: C, 66.37; H, 7.08; N, 6.25.

## EXAMPLE 26

6-(*trans*-4-{[Ethyl-[3-(4-fluorophenyl)propyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one



Coupling of 6-{*trans*-4-[3-(4-trifluoromethylphenyl)propylamino]-cyclohexyl}-3*H*-benzoxazol-2-one (200 mg, 0.48 mmol) and acetaldehyde (42 mg, 0.96 mmol) following the procedure described in Example 24, followed by formation of the HCl salt, gave 6-(*trans*-4-{[ethyl-[3-(4-fluorophenyl)propyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one (80 mg, 35%), as an off-white solid: mp 248-252°C; IR (KBr): 2946, 1771, 1497, 1451 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 11.49 (s, 1H), 9.81 (br s, 1H), 7.68 (d, *J* = 8 Hz, 2H), 7.51 (d, *J* = 8 Hz, 2H), 7.16 (s, 1H), 7.00 (s, 1H), 3.40-3.31 (m, 1H), 3.27-3.09 (m, 3H), 3.09-2.99 (m, 1H), 2.77 (q, *J* = 7, 3 Hz, 2H), 2.59-2.50 (m, 1H), 2.15-2.00 (m, 4H), 1.92-1.88 (m, 2H), 1.69-1.54 (m, 4H), 1.27 (t, *J* = 7 Hz, 3H); CI-MS

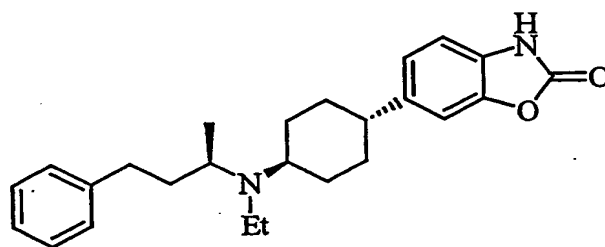
-58-

(methane) ( $m/z$ ): 447  $[M + H]^+$ ; calcd for  $C_{25}H_{29}F_3N_2O_2$ , 447.2259; found, 447.2267; HPLC: method C, 14.40 minutes (98.3%); method D, 16.11 minutes (98.5%); Anal. Calcd for  $C_{25}H_{29}F_3N_2O_2 \cdot HCl \cdot 0.25H_2O$ : C, 61.60; H, 6.31; N, 5.75. Found: C, 61.59; H, 6.22; N, 5.58.

5

## EXAMPLE 27

6-(*trans*-4-{Ethyl-[(*R*)-1-methyl-3-phenylpropyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one



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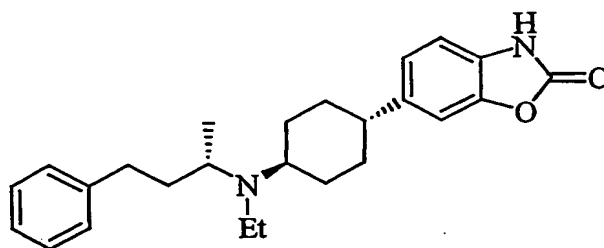
20

Coupling of 6-{*trans*-4-[(*R*)-1-methyl-3-phenylpropylamino]cyclohexyl}-3*H*-benzoxazol-2-one (370 mg, 1.01 mmol) and acetaldehyde (44 mg, 1.01 mmol) following the procedure described in Example 24, followed by formation of the HCl salt, gave 6-(*trans*-4-{ethyl-[(*R*)-1-methyl-3-phenylpropyl]amino}-cyclohexyl)-3*H*-benzoxazol-2-one (70 mg, 25%), as a pale yellow solid (a mixture of diastereomers): mp 139-158°C; IR (KBr): 2941, 1772, 1497, 1451  $cm^{-1}$ ;  $^1H$  NMR (500 MHz, DMSO- $d_6$ ):  $\delta$  11.52 (s, 2H), 9.11 (s, 2H), 7.35-7.21 (m, 10H), 7.18 (m, 4H), 7.00 (s, 2H), 3.20 (m, 2H), 2.81 (m, 2H), 2.54 (m, 2H), 2.20-1.51 (m, 28H), 1.44 (d,  $J = 7$  Hz, 3H), 1.32 (d,  $J = 7$  Hz, 3H), 1.26 (m, 6H); API-MS (methane) ( $m/z$ ): 393  $[M + H]^+$ ; calcd for  $C_{25}H_{32}N_2O_2$ , 393.2542; found, 393.2540; HPLC: method C, 5.77 minutes (97.4%), method D, 11.47 minutes and 11.57 minutes (98.1%); Anal. Calcd for  $C_{25}H_{32}N_2O_2 \cdot HCl \cdot 0.5H_2O$ : C, 68.55; H, 7.82; N, 6.40. Found: C, 68.67; H, 8.03; N, 6.27.

## EXAMPLE 28

6-(*trans*-4-{Ethyl-[(*S*)-1-methyl-3-phenylpropyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one

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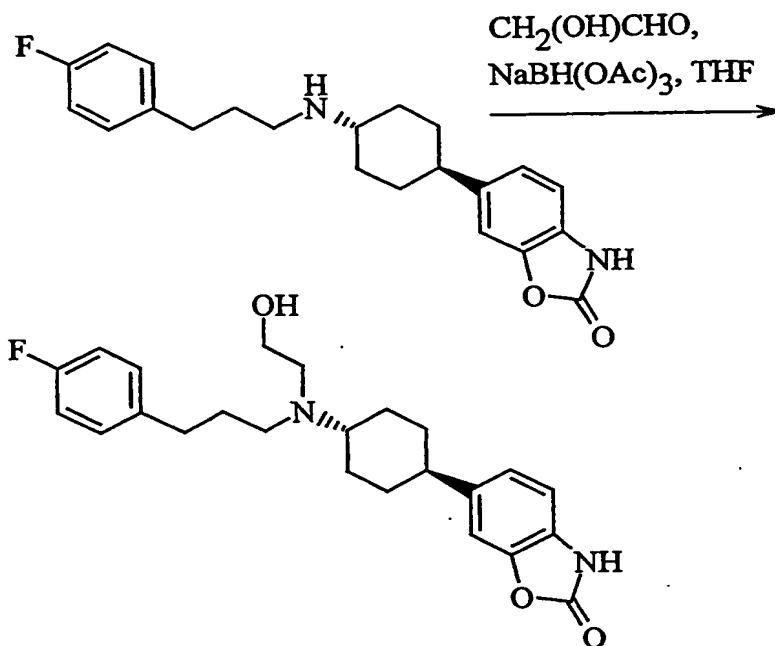


Coupling of 6-{*trans*-4-[(*S*)-1-methyl-3-phenylpropylamino]cyclohexyl}-3*H*-benzoxazol-2-one (196 mg, 0.538 mmol) and acetaldehyde (24 mg, 0.538 mmol) following the procedure described in Example 24, followed by formation of the HCl salt, gave 6-(*trans*-4-{ethyl-[(*S*)-1-methyl-3-phenylpropyl]-amino}cyclohexyl)-3*H*-benzoxazol-2-one (110 mg, 50%), as a pale yellow solid (a mixture of diastereomers): mp 221-246°C; IR (KBr): 3424, 2929, 1771, 1495 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 11.52 (s, 2H), 9.11 (s, 2H), 7.35-7.21 (m, 10H), 7.18 (m, 4H), 7.00 (s, 2H), 3.20 (m, 2H), 2.81 (m, 2H), 2.54 (m, 2H), 2.20-1.51 (m, 28H), 1.44 (d, *J* = 7 Hz, 3H), 1.32 (d, *J* = 7 Hz, 3H), 1.26 (m, 6H); API-MS (methane) (*m/z*): 393 [M + H]<sup>+</sup>; HPLC: method C, 5.88 minutes (97.4%), method D, 11.32 minutes (>99%); Anal. Calcd for C<sub>25</sub>H<sub>32</sub>N<sub>2</sub>O<sub>2</sub>·HCl·H<sub>2</sub>O: C, 67.17; H, 7.89; N, 6.27. Found: C, 67.18; H, 7.69; N, 5.98.

## EXAMPLE 29

6-{*trans*-4-[[3-(4-Fluorophenyl)propyl]-(2-hydroxyethyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one

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To a stirred solution of 6-{*trans*-4-[3-(4-fluorophenyl)propylamino]-cyclohexyl}-3*H*-benzoxazol-2-one (0.5 g, 1.2 mmol) in THF (25 mL) and CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added Et<sub>3</sub>N (0.17 mL, 1.2 mmol), glycoaldehyde (110 mg, 1.8 mmol), and 3Å molecular sieves. After stirring the reaction mixture for 5 to 10 minutes, NaBH(OAc)<sub>3</sub> was added, and stirring was continued for 0.5 hours. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in MeOH. The solution was brought to pH = 11 with 2N NaOH, filtered through Celite, and concentrated under reduced pressure. Purification by flash chromatography (silica, 90:9.5:0.5 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH) and (silica, 90:10 CH<sub>2</sub>Cl<sub>2</sub>:MeOH) resulted in isolation of the free base (120 mg, 24%).

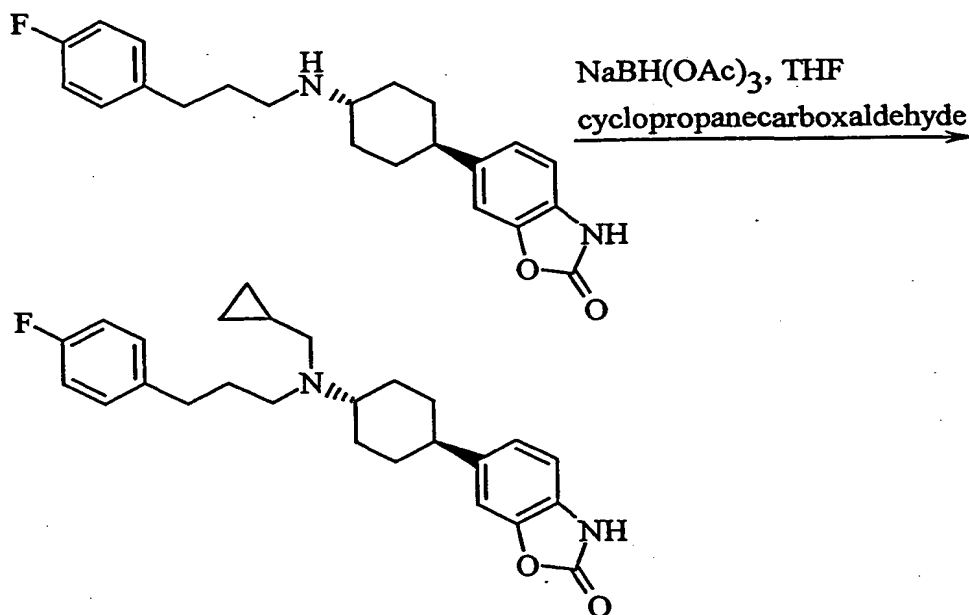
Formation of the HCl salt gave compound 6-{*trans*-4-[[3-(4-fluorophenyl)propyl]-(2-hydroxyethyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one as a white solid: mp 259-262°C; IR (KBr): 3314, 2949, 1765, 1509 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 11.50 (s, 1H), 9.40 (br s, 1H), 7.32-7.28 (m, 2H), 7.18-7.12 (m, 3H), 7.00 (s, 2H), 5.34-5.31 (m, 1H), 3.76-3.74 (m, 2H), 3.49-3.39 (m, 1H), 3.21-3.08 (m, 3H), 2.65 (t, *J* = 8 Hz, 2H), 2.60-2.49 (m, 2H), 2.18-1.99 (m, 4H), 1.98-1.86 (m, 2H), 1.71-1.52 (m, 4H); API-MS (methane) (*m/z*): 413 [M + H]<sup>+</sup>; calcd for C<sub>24</sub>H<sub>29</sub>FN<sub>2</sub>O<sub>3</sub>, 413.2240; found, 413.2239; HPLC: method A,

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5.47 minutes (98.9%); method B, 11.11 minutes (98.5%); Anal. Calcd for  $C_{24}H_{29}FN_2O_3 \cdot HCl \cdot 0.5H_2O$ : C, 62.94; H, 6.82; N, 6.12. Found: C, 63.10; H, 6.67; N, 6.06.

## EXAMPLE 30

5 6-(*trans*-4-{Cyclopropylmethyl-[3-(4-fluorophenyl)propyl]amino}cyclohexyl)-  
3*H*-benzoxazol-2-one



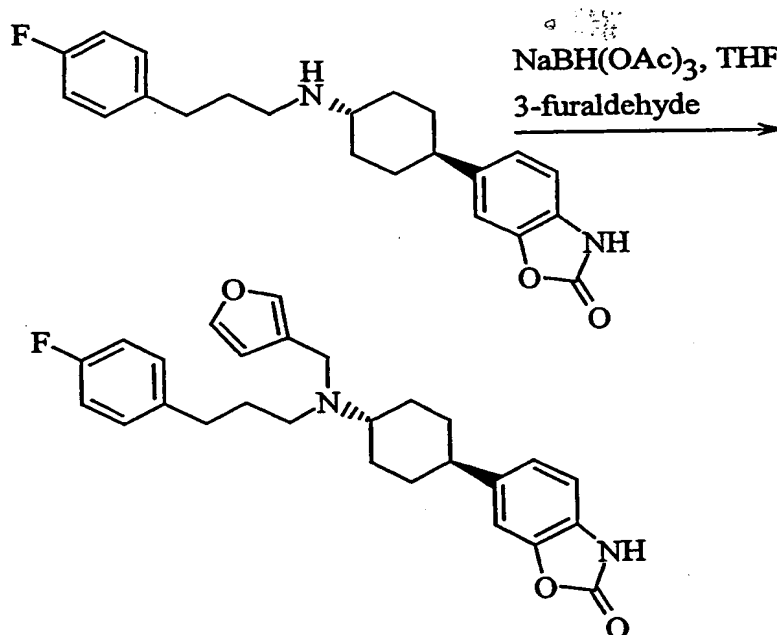
The free base of 6-{*trans*-4-[3-(4-fluorophenyl)propylamino]cyclohexyl}-  
3*H*-benzoxazol-2-one (400 mg, 0.99 mmol) was made by the addition of 1*N*  
NaOH (0.99 mL, 0.99 mmol) to 6-{*trans*-4-[3-(4-fluorophenyl)propylamino]-  
cyclohexyl}-3*H*-benzoxazol-2-one hydrochloride in THF (25 mL) and MeOH  
(10 mL). Cyclopropanecarboxaldehyde (70 mg, 0.99 mmol) was added, followed  
by NaBH(OAc)<sub>3</sub> (300 mg, 1.4 mmol). Additional NaBH(OAc)<sub>3</sub> and  
cyclopropanecarboxaldehyde were added at intervals, over 28 hours, to drive the  
reaction to completion. The solution was brought to pH = 11 with solid NaOH and  
then concentrated under reduced pressure. Purification by flash chromatography  
(silica, 90:9.5:0.5 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH) followed by formation of the HCl salt  
gave 6-(*trans*-4-{cyclopropylmethyl-[3-(4-fluorophenyl)propyl]amino}-  
cyclohexyl)-3*H*-benzoxazol-2-one (347 mg, 76%), as a white solid: mp 221-

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225°C; IR (KBr): 2937, 1764, 1510  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  11.50 (s, 1H), 9.78 (br s, 1H), 7.33-7.29 (m, 2H), 7.18-7.12 (m, 3H), 7.02 (s, 2H), 3.50-3.42 (m, 1H), 3.24-2.97 (m, 4H), 2.72-2.61 (m, 2H), 2.59-2.55 (m, 1H), 2.18-2.01 (m, 4H), 1.94-1.88 (m, 2H), 1.69-1.53 (m, 4H), 1.18-1.09 (m, 1H), 0.68-0.59 (m, 2H), 0.46-0.36 (m, 2H); ESI-MS ( $m/z$ ): 423  $[\text{M} + \text{H}]^+$ ; HPLC: method A, 6.22 minutes (98.5%); Anal. Calcd for  $\text{C}_{26}\text{H}_{31}\text{FN}_2\text{O}_2 \cdot \text{HCl}$ : C, 68.04; H, 7.03; N, 6.10. Found: C, 67.65; H, 7.07; N, 5.95.

## EXAMPLE 31

6-(*trans*-4-{[3-(4-Fluorophenyl)propyl]furan-3-ylmethylamino}cyclohexyl)-3*H*-benzoxazol-2-one



The free base of 6-{*trans*-4-[3-(4-fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one was made by the addition of  $\text{K}_2\text{CO}_3$  (170 mg, 1.2 mmol) to 6-{*trans*-4-[3-(4-fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one hydrochloride (500 mg, 1.2 mmol) in THF (50 mL). To this suspension was added 3-furaldehyde (470 mg, 4.9 mmol) and, after 10 minutes,  $\text{NaBH}(\text{OAc})_3$  (520 mg, 2.4 mmol) was added. After stirring the reaction mixture 3 hours, additional  $\text{NaBH}(\text{OAc})_3$  (520 mg, 2.4 mmol) was added, and stirring continued for 14.5 hours. The solution was diluted with MeOH and brought to pH = 13 with

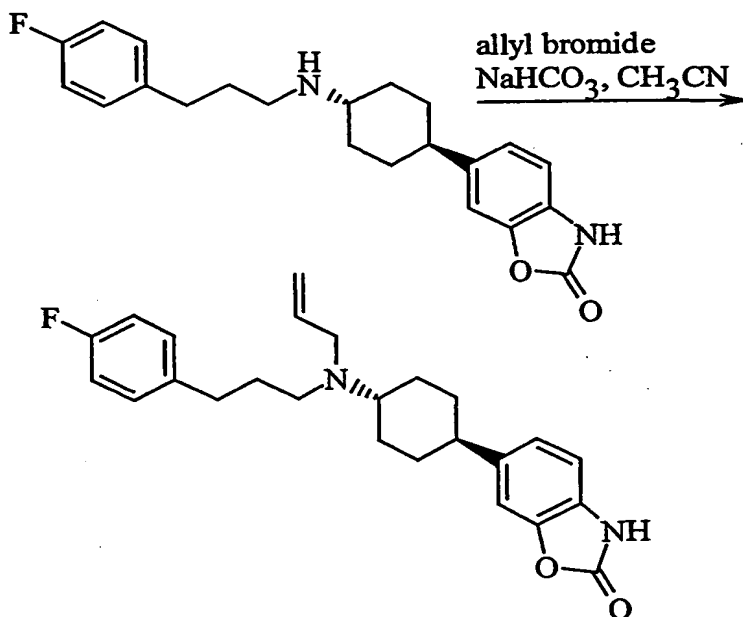
-63-

solid NaOH. The solution was then concentrated under reduced pressure.

Purification by flash chromatography (silica, 90:9.5:0.5 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH), followed by formation of the HCl salt, gave 6-(*trans*-4-{{3-(4-fluorophenyl)-propyl}furan-3-ylmethylamino}cyclohexyl)-3*H*-benzoxazol-2-one (272 mg, 46%) as an off-white solid: mp 225-227°C; IR (KBr): 2929, 1773, 1510 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 11.49 (s, 1H), 9.99 (br s, 1H), 7.90 (s, 1H), 7.76 (s, 1H), 7.27-7.24 (m, 2H), 7.18 (s, 1H), 7.14-7.10 (m, 2H), 7.02-6.98 (m, 2H), 6.75 (s, 1H), 4.30-4.18 (m, 2H), 3.33-3.29 (m, 1H), 3.20-3.12 (m, 1H), 3.01-2.93 (m, 1H), 2.67-2.53 (m, 3H), 2.22-2.15 (m, 2H), 2.07-1.88 (m, 4H), 1.78-1.66 (m, 2H), 1.62-1.49 (m, 2H); ESI-MS (*m/z*): 449 [M + H]<sup>+</sup>; HPLC: method A, 6.27 minutes (99.8%); Anal. Calcd for C<sub>27</sub>H<sub>29</sub>FN<sub>2</sub>O<sub>3</sub>·HCl: C, 66.87; H, 6.23; N, 5.78. Found: C, 66.54; H, 6.27; N, 5.48.

## EXAMPLE 32

6-(*trans*-4-{Allyl-[3-(4-fluorophenyl)propyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one



To a stirred suspension of 6-(*trans*-4-[3-(4-fluorophenyl)-propylamino]-cyclohexyl)-3*H*-benzoxazol-2-one (400 mg, 0.99 mmol) in THF (40 mL) and DMF (3 mL) was added NaHCO<sub>3</sub> (180 mg, 2.2 mmol) and allyl bromide



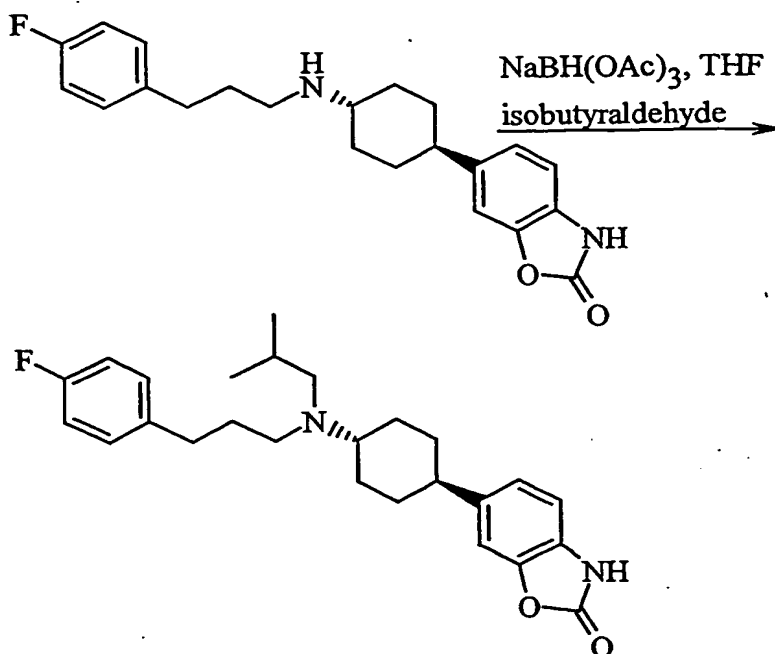
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(130 mg, 1.1 mmol). After refluxing overnight, additional DMF (1.5 mL), allyl bromide (30 mg, 29 mmol), and NaHCO<sub>3</sub> (21 mg, 0.25 mmol) were added. The reaction mixture was refluxed for 12 hours and then cooled to room temperature. The material was diluted with water and extracted with EtOAc (3X). The combined organics were washed with water, saturated NaCl solution (3X), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 90:10 CH<sub>2</sub>Cl<sub>2</sub>:MeOH), followed by formation of the HCl salt, gave 6-(*trans*-4-{allyl-[3-(4-fluorophenyl)propyl]-amino}cyclohexyl)-3*H*-benzoxazol-2-one (138 mg, 31%), as a white solid: mp 224-230°C; IR (KBr): 2943, 1770, 1510 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 11.51 (s, 1H), 10.38 (br s, 1H), 7.31-7.28 (m, 2H), 7.17-7.11 (m, 3H), 7.00 (s, 2H), 6.11-6.04 (m, 1H), 5.55 (d, *J* = 17 Hz, 1H), 5.45 (d, *J* = 10 Hz, 1H), 3.87-3.71 (m, 2H), 3.38-3.31 (m, 1H), 3.19-3.13 (m, 1H), 3.05-2.92 (m, 1H), 2.70-2.51 (m, 3H), 2.18-2.12 (m, 2H), 2.07-1.99 (m, 2H), 1.92-1.87 (m, 2H), 1.72-1.50 (m, 4H); (ESI-MS (*m/z*): 409 [M + H]<sup>+</sup>; HPLC: method B, 11.34 minutes (98.1%); Anal. Calcd for C<sub>25</sub>H<sub>29</sub>FN<sub>2</sub>O<sub>2</sub>·HCl: C, 67.48; H, 6.80; N, 6.30. Found: C, 67.29; H, 6.93; N, 6.07.

## EXAMPLE 33

6-(*trans*-4-{[3-(4-Fluorophenyl)propyl]isobutylamino}cyclohexyl)-3*H*-benzoxazol-2-one

-65-



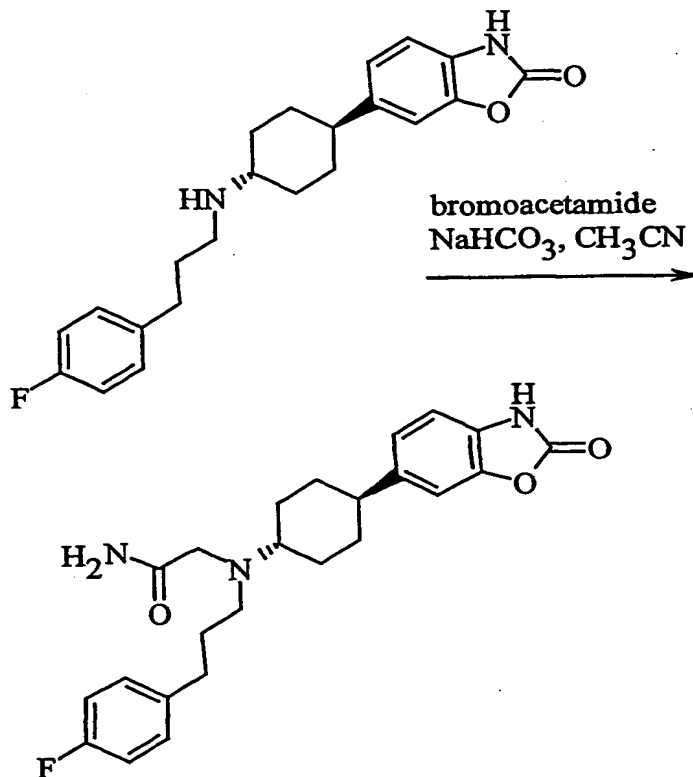
The free base of 6-{*trans*-4-[3-(4-fluorophenyl)-propylamino]cyclohexyl}-3*H*-benzoxazol-2-one was made by the addition of K<sub>2</sub>CO<sub>3</sub> (140 mg, 1.0 mmol) to 6-{*trans*-4-[3-(4-fluorophenyl)propylamino]-cyclohexyl}-3*H*-benzoxazol-2-one hydrochloride (400 mg, 1.0 mmol) in THF (40 mL). The solution was warmed to dissolve the free base and then cooled to room temperature. Isobutyraldehyde (280 mg, 4.0 mmol) was added, followed by NaBH(OAc)<sub>3</sub> (420 mg, 2.0 mmol) after 10 minutes. The reaction mixture was stirred for 2.5 days and then concentrated under reduced pressure. The solution was diluted with MeOH and brought to pH = 10 with solid NaOH. The solution was then concentrated under reduced pressure. Purification by flash chromatography (silica, 95:4.75:0.25 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH), followed by formation of the HCl salt, gave 6-{*trans*-4-[[3-(4-fluorophenyl)propyl]-isobutylamino}cyclohexyl}-3*H*-benzoxazol-2-one (327 mg, 46%), as a white solid: mp 199-201°C; IR (KBr): 2941, 1769, 1510 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 11.51 (s, 1H), 9.16 (br s, 1H), 7.32-7.29 (m, 2H), 7.17-7.12 (m, 3H), 6.99 (s, 2H), 3.38-3.33 (m, 1H), 3.13-3.03 (m, 3H), 2.86-2.80 (m, 1H), 2.66-2.62 (m, 2H), 2.58-2.51 (m, 1H), 2.13-1.97 (m, 5H), 1.92-1.87 (m, 2H), 1.74-1.56 (m, 4H), 1.02-0.98 (m, 6H); ESI-MS (*m/z*): 425 [M + H]<sup>+</sup>; HPLC: method A, 6.38 minutes (98.7%); Anal. Calcd for

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$C_{26}H_{33}FN_2O_2 \cdot HCl$ : C, 67.74; H, 7.43; N, 6.08. Found: C, 67.65; H, 7.29; N, 5.93.

## EXAMPLE 34

2-{{[3-(4-Fluorophenyl)propyl]-[4-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-cyclohexyl]amino}acetamide



To a stirred suspension of 6-{*trans*-4-[3-(4-fluorophenyl)propylamino]-cyclohexyl}-3*H*-benzoxazol-2-one (110 mg, 0.81 mmol) in DMF (15 mL) was added NaHCO<sub>3</sub> (140 mg, 1.6 mmol) and bromoacetamide (300 mg, 0.74 mmol).

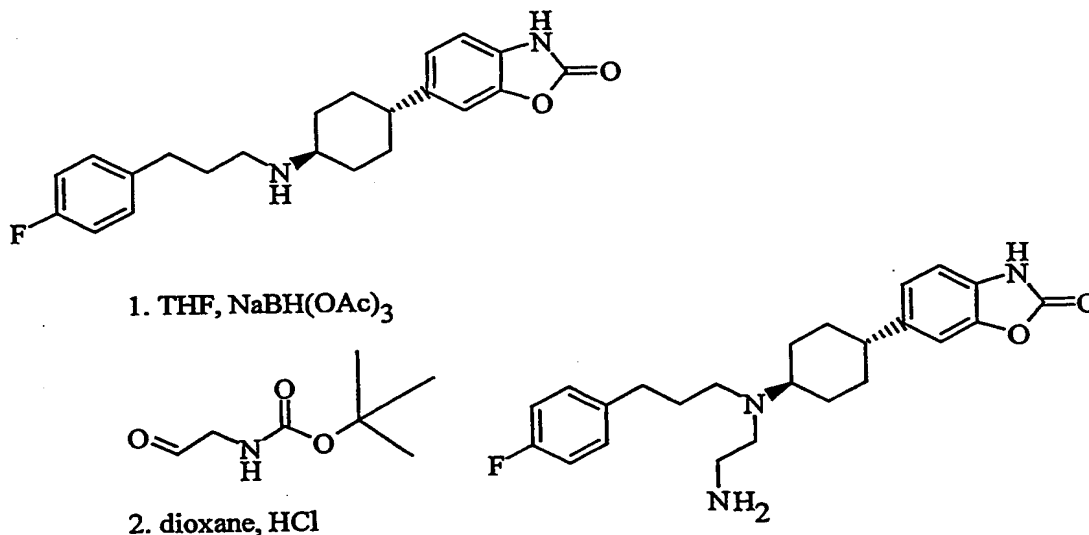
After 16 hours the reaction mixture was warmed to 50°C. After 4 hours, additional bromide (150 mg, 0.37 mmol) and NaHCO<sub>3</sub> (31 mg, 0.37 mmol) were added, and the temperature was increased to 75°C. After 4 hours, the reaction mixture was cooled to room temperature, diluted with water and extracted with EtOAc. The combined organics were washed with water, saturated NaCl, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 95:4.75:0.25 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH) followed by

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conversion to the HCl salt gave compound 2-{[3-(4-fluorophenyl)propyl]-[4-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-cyclohexyl]amino}acetamide (60 mg, 17%), as a white solid: mp 266-270°C; IR (KBr): 3331, 3149, 2943, 1762, 1691  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  11.47 (s, 1H), 9.08 (br s, 1H), 7.96 (br s, 1H), 7.73 (br s, 1H), 7.29-7.25 (m, 2H), 7.17-7.01 (m, 3H), 6.99 (s, 2H), 4.05-4.02 (m, 1H), 3.81-3.78 (m, 1H), 3.47-3.38 (m, 1H), 3.22-3.12 (m, 3H), 2.63 (t,  $J = 8$  Hz, 2H), 2.57-2.52 (m, 1H), 2.14-1.87 (m, 6H), 1.71-1.49 (m, 4H); ESI-MS ( $m/z$ ): 426  $[\text{M} + \text{H}]^+$ ; HPLC: method A, 5.44 minutes (98.0%); HPLC: method E, 6.50 minutes (>99%); Anal. Calcd for  $\text{C}_{24}\text{H}_{28}\text{FN}_3\text{O}_3 \cdot \text{HCl}$ : C, 61.80; H, 6.37; N, 9.01. Found: C, 61.78; H, 6.27; N, 8.80.

## EXAMPLE 35

6-(*trans*-4-{(2-Aminoethyl)-[3-(4-fluorophenyl)propyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one



To a stirred solution of 6-{*trans*-4-[3-(4-fluorophenyl)propylamino]-cyclohexyl}-3*H*-benzoxazol-2-one (HCl salt) (0.5 g, 1.2 mmol) in THF (25 mL) was added  $\text{Et}_3\text{N}$  (0.19 mL, 1.4 mmol), *tert*-butyl *N*-(2-oxoethyl)carbamate (220 mg, 1.9 mmol) and 3 Å molecular sieves. After stirring the reaction mixture for 10 minutes,  $\text{NaBH}(\text{OAc})_3$  (0.43 g, 0.39 mmol) was added, and stirring was continued for 5.75 hours. The reaction mixture was diluted with MeOH, brought to pH = 8 with 1N NaOH, filtered, and concentrated under reduced pressure.

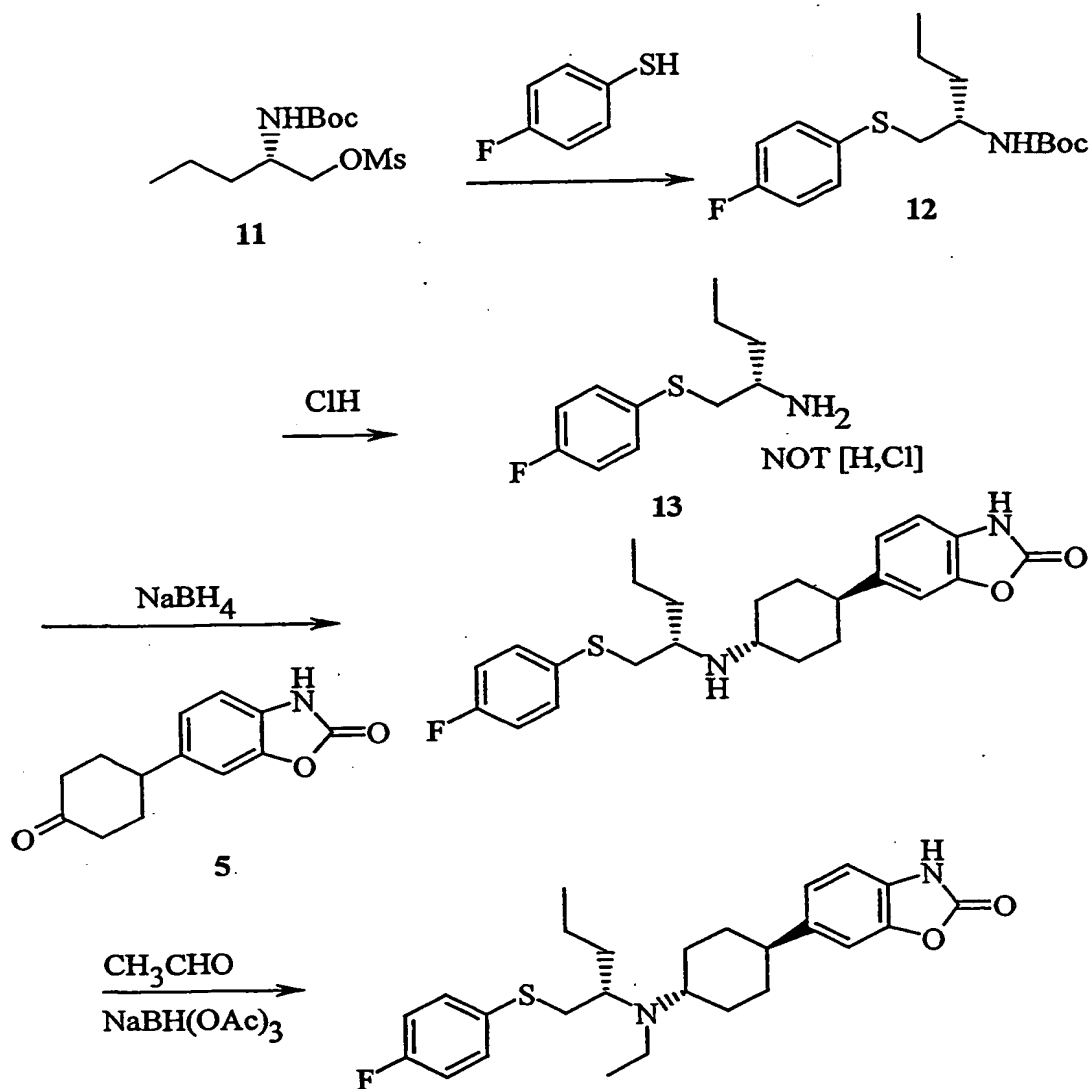
-68-

Purification by flash chromatography (silica, 95:5 CH<sub>2</sub>Cl<sub>2</sub>:MeOH) gave 220 mg of Boc protected amine. The residue was dissolved in dioxane (12 mL), and 4 M HCl in dioxane (2 mL) was added. The mixture was stirred for 2 hours, concentrated under reduced pressure, and purified by flash chromatography (silica, 89:10:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH). Formation of the HCl salt gave 6-(*trans*-4-((2-aminoethyl)-[3-(4-fluorophenyl)propyl]amino)cyclohexyl)-3*H*-benzoxazol-2-one (133 mg, 27%), as a white solid: mp 161-169°C; IR (KBr): 2929, 1764, 1656 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 7.24-7.22 (m, 2H), 7.10-7.06 (m, 3H), 6.95-6.90 (m, 2H), 3.50-3.10 (br s, 3H), 2.60-2.41 (m, 10H), 1.83-1.76 (m, 4H), 1.79-1.63 (m, 2H), 1.49-1.31 (m, 4H); ESI-MS (*m/z*): 412 [M + H]<sup>+</sup>; Anal. Calcd for C<sub>24</sub>H<sub>30</sub>FN<sub>3</sub>O<sub>2</sub>: C, 70.05; H, 7.35; N, 10.21. Found: C, 69.86; H, 7.45; N, 10.07.

## EXAMPLE 36

- (a) (*S*)-6-{*trans*-4-[1-(4-Fluorophenylsulfanyl)pentan-2-ylamino]cyclohexyl}-3*H*-benzoxazol-2-one
- (b) (*S*)-6-{*trans*-4-[Ethyl(1-(4-fluorophenylsulfanyl)pentan-2-yl)amino]-cyclohexyl}-3*H*-benzoxazol-2-one

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**Step 1:** To a stirred solution of mesylate 11 (2.23 g, 7.95 mmol) and 4-fluorobenzenethiol (1.02 g, 7.95 mmol) in THF/2-PrOH (30 mL, 1:1) was added sodium borohydride (0.39 g, 10.34 mmol). The reaction mixture was stirred overnight then diluted with EtOAc (100 mL) and washed successively with 20% KOH (3 × 30 mL), water (30 mL), and saturated NaCl (30 mL). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure.

Purification by flash chromatography (silica, 7:1 Hexanes/EtOAc) gave Boc-protected amine 12 (1.24 g, 50%), as a white solid: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.38 (dd, *J* = 7, 4 Hz, 2H), 6.98 (t, *J* = 4 Hz, 2H), 4.51 (br s, 1H), 3.84 (br s, 1H), 3.01 (m, 2H), 1.57 (m, 2H), 1.54 (s, 9H), 1.37 (m, 2H), 0.89 (t, *J* = 4 Hz, 3H).

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Step 2: To a stirred solution of Boc-amine 12 (1.24 g, 3.96 mmol) in dioxane (5 mL) was added HCl in dioxane (1.48 mL of a 4M solution, 5.92 mmol). The reaction mixture was concentrated under reduced pressure after 1 hour to give amine 13 (0.93 g, 94%), as a white solid:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.65 (br s, 2H), 7.55 (dd,  $J = 7, 4$  Hz, 2H), 6.99 (t,  $J = 4$  Hz, 2H), 3.29-3.13 (m, 3H), 1.84 (m, 2H), 1.38 (m, 2H), 0.88 (t,  $J = 4$  Hz, 3H).

Step 3: To a stirred solution of amine 13 (0.93 g, 3.72 mmol) in 2-PrOH (30 mL) was added 4Å molecular sieves and ketone 5 (0.88 g, 3.72 mmol). The reaction mixture was stirred for 3 hours. Sodium borohydride (0.19 g, 5.21 mmol) was added, and the mixture was stirred overnight. The reaction mixture was filtered and concentrated under reduced pressure. Purification by flash chromatography (silica, 1.5:1 Hexanes/EtOAc) gave (a) (S)-6-{*trans*-4-[1-(4-fluorophenylsulfanyl)pentan-2-ylamino]cyclohexyl}-3*H*-benzoxazol-2-one (282 mg, 17%), as a white solid:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.40 (m, 2H), 7.01-6.93 (m, 5H), 3.07-2.81 (m, 3H), 2.47 (m, 2H), 1.93-1.71 (m, 4H), 1.57-1.14 (m, 8H), 0.87 (t,  $J = 6$  Hz, 3H).

Step 4: To (a) (S)-6-{*trans*-4-[1-(4-fluorophenylsulfanyl)pentan-2-ylamino]cyclohexyl}-3*H*-benzoxazol-2-one (292 mg, 0.687 mmol) in THF (10 mL) was added acetaldehyde (30 mg, 0.68 mmol) and 4Å molecular sieves. After stirring for 0.25 hours, sodium triacetoxyborohydride (204 mg, 0.962 mmol) was added. The reaction mixture was stirred for 0.75 hours then concentrated under reduced pressure. The crude residue was taken up in methanol (10 mL), and solid NaOH was added until the pH was  $>8$ . The solution was concentrated under reduced pressure. Purification by flash chromatography (silica, 1:1 Hexanes:EtOAc) gave (b) (S)-6-{*trans*-4-[ethyl(1-(4-fluorophenylsulfanyl)pentan-2-yl)amino]cyclohexyl}-3*H*-benzoxazol-2-one (210 mg, 67%), as a clear oil: IR (KBr): 3219, 2926, 1764, 1589  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.34 (m, 2H), 7.05-6.92 (m, 5H), 3.02 (m, 3H), 2.79 (m, 1H), 2.64 (m, 6H), 2.38 (m, 1H), 1.93-1.78 (m, 4H), 1.47-1.29 (m, 4H), 0.93 (t,  $J = 5$  Hz, 3H), 0.89 (t,  $J = 6$  Hz, 3H); API-MS ( $m/z$ ): 457  $[\text{M} + \text{H}]^+$ ; calcd for  $\text{C}_{26}\text{H}_{33}\text{FN}_2\text{O}_2\text{S}$ ,

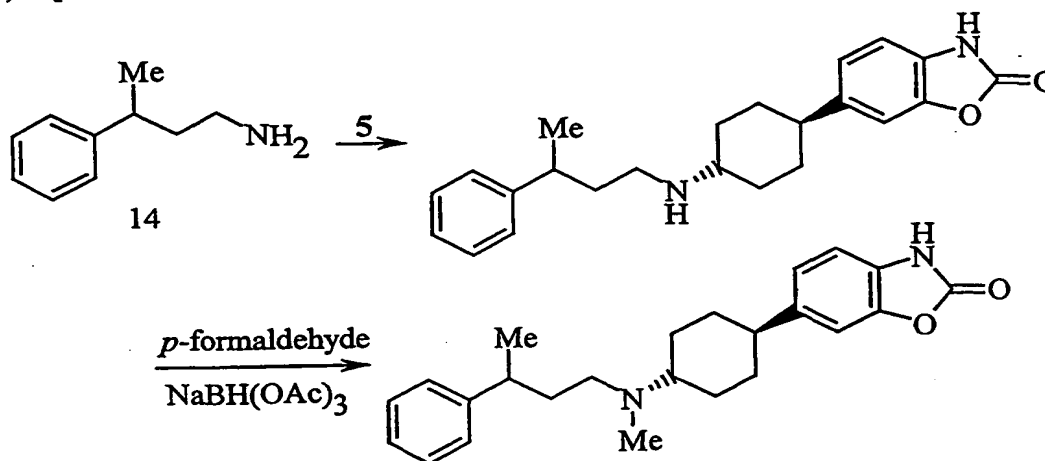
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457.2325; found, 457.2324; HPLC: method C, 6.55 minutes (>99%), method D, 12.37 minutes (>99%).

## EXAMPLE 37

(a) 6-[*trans*-4-(3-Phenylbutylamino)cyclohexyl]-3*H*-benzoxazol-2-one

5 (b) 6-[*trans*-4-(Methyl-3-phenylbutylamino)cyclohexyl]-3*H*-benzoxazol-2-one



**Step 1:** To a stirred solution of amine 14 (1.3 g, 6.2 mmol) in THF (75 mL) was added 5 (1.44 g, 6.22 mmol). The reaction mixture was stirred for 1 hour, NaBH<sub>4</sub> (329 mg, 8.71 mmol) was added followed by water (30 mL). The reaction mixture was stirred for 45 minutes then diluted with EtOAc. The mixture was washed with 1N HCl and concentrated under reduced pressure. Purification by flash chromatography (silica, 95:5:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH) gave 6-[*trans*-4-(3-phenylbutylamino)cyclohexyl]-3*H*-benzoxazol-2-one (640 mg, 28%), as a white solid: <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.31-7.11 (m, 7H), 6.94 (s, 1H), 2.78 (m, 1H), 2.45-2.35 (m, 5H), 1.87 (br d, *J* = 10 Hz, 2H), 1.73 (br d, *J* = 10 Hz, 2H), 1.68 (m, 2H), 1.44 (dddd, *J* = 10, 10, 10, 2 Hz, 2H), 1.19 (d, *J* = 4 Hz, 3H), 1.08 (dddd, *J* = 10, 10, 10, 2 Hz, 2H).

**Step 2:** To a stirred solution of 6-[*trans*-4-[3-phenylbutylamino]-cyclohexyl]-3*H*-benzoxazol-2-one (638 mg, 1.75 mmol) in MeOH (10 mL) containing water (0.5 mL) was added *p*-formaldehyde (263 mg, 8.76 mmol). The reaction mixture was stirred for 2 hours, and NaBH<sub>4</sub> (519 mg, 2.45 mmol) was added. The reaction mixture was stirred for 3 hours. The reaction was treated with



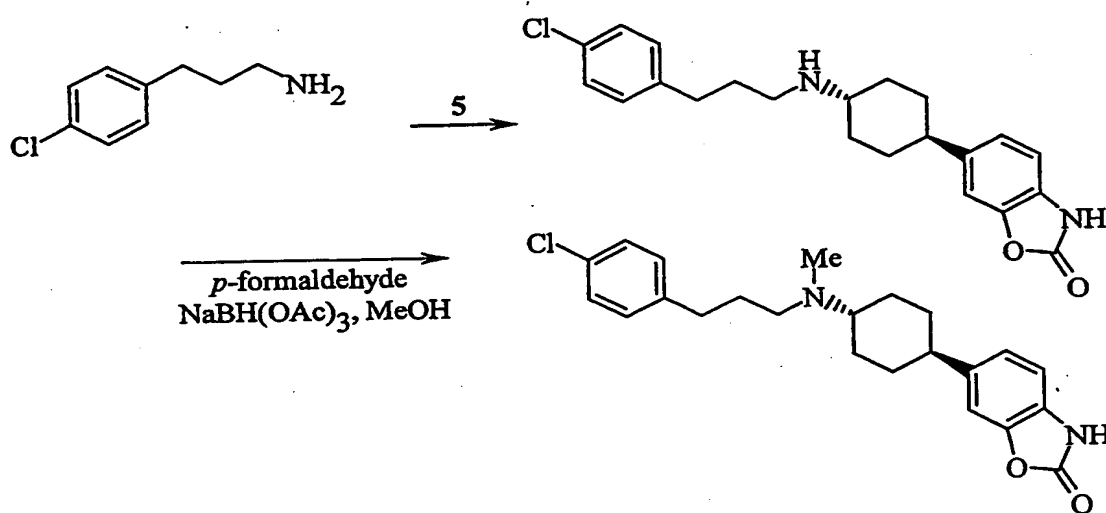
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solid NaOH until a clear solution resulted and concentrated under reduced pressure. Purification by flash chromatography (95:5:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH) gave 6-[*trans*-4-(methyl-3-phenylbutylamino)cyclohexyl]-3*H*-benzoxazol-2-one (231 mg, 35%), as a white solid: mp 61-70°C; IR (KBr): 2928, 1774 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 7.29-7.12 (m, 7H), 6.97 (s, 1H), 2.76 (m, 1H), 2.49-2.26 (m, 5H), 2.14 (s, 3H), 1.77 (m, 4H), 1.67 (m, 2H), 1.43 (m, 2H), 1.27 (m, 2H), 1.17 (d, J = 4 Hz, 3H); API-MS (*m/z*): 379 [M + H]<sup>+</sup>; HPLC: method A, 5.99 minutes (94.3%); HPLC: method B, 10.97 minutes (>99%); Anal. Calcd for C<sub>24</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>·0.5H<sub>2</sub>O: C, 74.39; H, 8.06; N, 7.23. Found: C, 74.41; H, 7.90; N, 7.31.

## EXAMPLE 38

(a) 6-{*trans*-4-[3-(4-Chlorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one

(b) 6-(*trans*-4-{[3-(4-Chlorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one



**Step 1:** To a solution of 3-(4-chlorophenyl)-1-propylamine hydrochloride (1.5 g, 7.3 mmol) in 2-propanol (50 mL) was added Et<sub>3</sub>N (1.1 mL, 8.0 mmol), ketone 5 (1.7 g, 7.3 mmol), THF (25 mL), and 3Å molecular sieves. The reaction mixture was warmed to dissolve ketone 5 and then stirred at room temperature for 2.25 hours. Sodium borohydride (550 mg, 14.5 mmol) was added, and the reaction

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mixture was stirred for 12 hours. The reaction was quenched with MeOH, and the mixture was filtered through a pad of Celite and concentrated under reduced pressure. Purification by flash chromatography (silica, 90:10 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) followed by trituration/recrystallization with MeOH gave 6-{*trans*-4-[3-(4-chlorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one (683 mg, 24%), as a white solid: <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 7.32 (d, *J* = 8 Hz, 2H), 7.23 (d, *J* = 8 Hz, 2H), 7.12 (s, 1H), 6.98-6.93 (m, 2H), 2.61 (t, *J* = 7 Hz, 2H), 2.56 (t, *J* = 7 Hz, 2H), 2.48-2.38 (m, 2H), 1.94 (br d, *J* = 10 Hz, 2H), 1.77 (br d, *J* = 10 Hz, 2H), 1.72-1.66 (m, 2H), 1.44 (dddd, *J* = 12, 12, 12, 3 Hz, 2H), 1.12 (dddd, *J* = 12, 12, 12, 3 Hz, 2H).

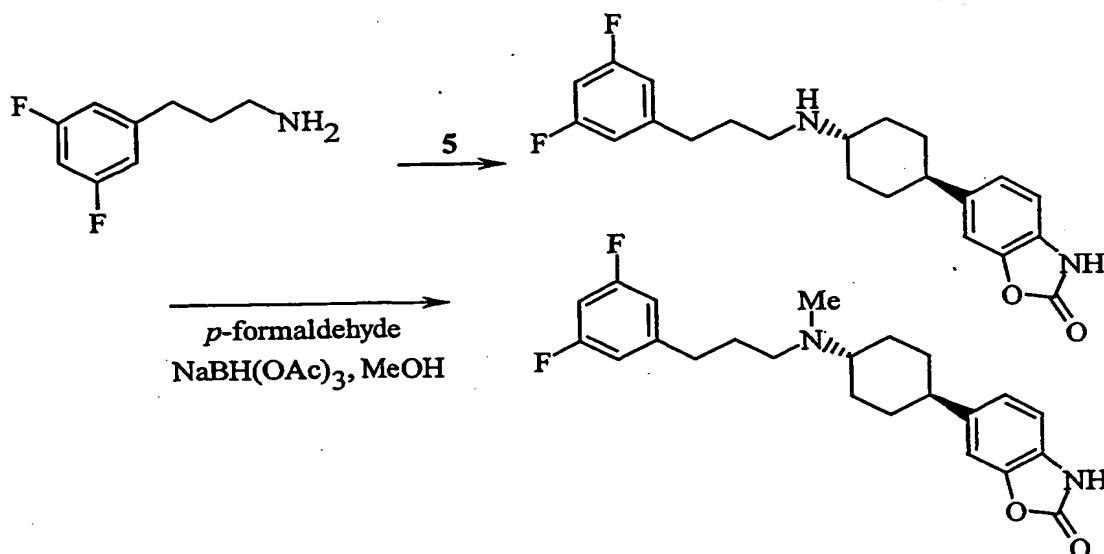
**Step 2:** To a stirred solution of 6-{*trans*-4-[3-(4-chlorophenyl)propylamino]-cyclohexyl}-3*H*-benzoxazol-2-one (655 mg, 1.7 mmol) in MeOH (20 mL) and CH<sub>2</sub>Cl<sub>2</sub> (25 mL) was added *p*-formaldehyde (0.70 mL of a 37 wt% solution in H<sub>2</sub>O, 8.5 mmol). The reaction mixture was warmed to dissolve compound the amine, and then stirred at room temperature for 15 minutes. NaBH(OAc)<sub>3</sub> was added and stirring was continued for 12 hours. The reaction mixture was brought to pH 8 with solid NaOH, concentrated under reduced pressure, and purified by flash chromatography (silica, 95:4.5:0.5 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH). Formation of the HCl salt, followed by recrystallization (MeOH:Et<sub>2</sub>O) gave 6-(*trans*-4-{[3-(4-chlorophenyl)propyl]-methylamino}-cyclohexyl)-3*H*-benzoxazol-2-one (461 mg, 66%), as a white solid: mp 267-271°C; IR (KBr): 2949, 1769, 1494, 1452 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 11.50 (s, 1H), 10.39 (s, 1H), 7.37 (d, *J* = 8 Hz, 2H), 7.30 (d, *J* = 8 Hz, 2H), 7.16 (s, 1H), 7.00 (br s, 2H), 3.33-3.26 (m, 1H), 3.18-3.10 (m, 1H), 3.04-2.95 (m, 1H), 2.69 (d, *J* = 5 Hz, 3H), 2.68-2.62 (m, 2H), 2.58-2.51 (m, 1H), 2.18-1.98 (m, 4H), 1.93-1.87 (m, 2H), 1.69-1.51 (m, 4H); HRMS-APCI (*m/z*): [M + H]<sup>+</sup> calcd for C<sub>23</sub>H<sub>27</sub>ClN<sub>2</sub>O<sub>2</sub>, 399.1839; found, 399.1831; HPLC: method A, 6.35 minutes (98.6%); method B, 11.82 minutes (99.1%); Anal. Calcd for C<sub>23</sub>H<sub>27</sub>ClN<sub>2</sub>O<sub>2</sub>·HCl·0.25H<sub>2</sub>O: C, 62.80; H, 6.53; N, 6.37. Found: C, 62.94; H, 6.57; N, 6.21.

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## EXAMPLE 39

(a) 6-(*trans*-4-[3-(3,5-Difluorophenyl)propylamino]cyclohexyl)-3*H*-benzoxazol-2-one

(b) 6-(*trans*-4-[[3-(3,5-Difluorophenyl)propyl]methylamino]cyclohexyl)-3*H*-benzoxazol-2-one



**Step 1:** Condensation of 3-(3,5-difluorophenyl)-1-propylamine (1.5 g, 6.5 mmol) and ketone 5 (1.5 g, 6.5 mmol), following the procedure described in Example 1, gave 6-(*trans*-4-[3-(3,5-difluorophenyl)propylamino]cyclohexyl)-3*H*-benzoxazol-2-one (640 mg, 26%), as a white solid: <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 7.13 (s, 1H), 7.01-6.92 (m, 5H), 2.66 (t, *J* = 8 Hz, 2H), 2.57 (t, *J* = 8 Hz, 2H), 2.49-2.40 (m, 2H), 1.95 (br d, *J* = 10 Hz, 2H), 1.78 (br d, *J* = 10 Hz, 2H), 1.74-1.68 (m, 2H), 1.45 (dddd, *J* = 13, 13, 13, 3 Hz, 2H), 1.14 (dddd, *J* = 13, 13, 13, 3 Hz, 2H).

**Step 2:** Condensation of 6-(*trans*-4-[3-(3,5-difluorophenyl)propylamino]cyclohexyl)-3*H*-benzoxazol-2-one (600 mg, 1.5 mmol) and *p*-formaldehyde (0.63 mL of a 37 wt% solution in H<sub>2</sub>O, 7.8 mmol), following the procedure described in Example 17 followed by conversion to the HCl salt, gave 6-(*trans*-4-[[3-(3,5-difluorophenyl)propyl]methylamino]cyclohexyl)-3*H*-benzoxazol-2-one (465 mg, 71%), as a white solid: mp 270-275°C; IR (KBr): 2950, 1762, 1626, 1596 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 11.49 (s, 1H), 10.15 (s, 1H),

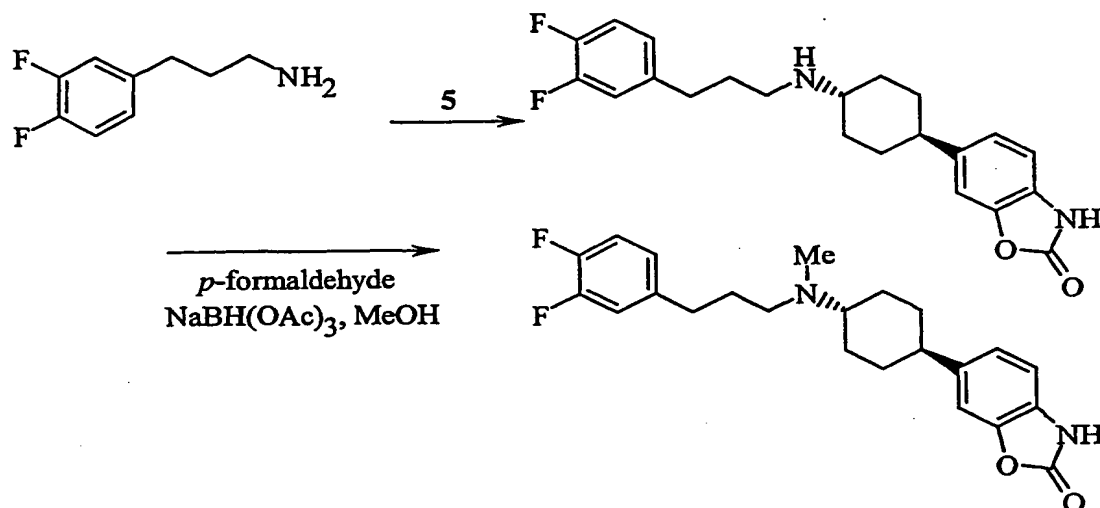
-75-

7.17 (s, 1H), 7.09-7.01 (m, 4H), 7.00 (s, 1H), 3.36-3.29 (m, 1H), 3.19-3.10 (m, 1H), 3.05-2.97 (m, 1H), 2.79-2.68 (m, 5H), 2.60-2.53 (m, 1H), 2.18-2.00 (m, 4H), 1.91 (br d,  $J = 11$  Hz, 2H), 1.69-1.51 (m, 4H); ESI ( $m/z$ ): 401  $[M + H]^+$ ; HPLC: method A, 6.42 minutes (98.2%); Anal. Calcd for  $C_{23}H_{26}F_2N_2O_2 \cdot HCl$ : C, 63.23; H, 6.23; N, 6.41. Found: C, 63.04; H, 6.33; N, 6.54.

## EXAMPLE 40

(a) 6-(*trans*-4-[3-(3,4-Difluorophenyl)propylamino]cyclohexyl)-3*H*-benzoxazol-2-one

(b) 6-(*trans*-4-{[3-(3,4-Difluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one



**Step 1:** Coupling of ketone 5 and 3-(3,4-difluorophenyl)-1-propylamine, using the method given in Example 1, gave 6-(*trans*-4-[3-(3,4-difluorophenyl)propylamino]cyclohexyl)-3*H*-benzoxazol-2-one (690 mg, 37%):  $^1H$  NMR (500 MHz,  $DMSO-d_6$ ):  $\delta$  7.33-7.24 (m, 2H), 7.12 (d,  $J = 1$  Hz, 1H), 7.06-7.02 (m, 1H), 6.98-6.93 (m, 2H), 3.51-3.10 (br s, 2H), 2.62 (dd,  $J = 8, 8$  Hz, 2H), 2.55 (dd,  $J = 7, 7$  Hz, 2H), 2.48-2.38 (m, 2H), 1.98-1.91 (m, 2H), 1.80-1.73 (m, 2H), 1.71-1.65 (m, 2H), 1.44 (dddd,  $J = 10, 10, 10, 3$  Hz, 2H), 1.13 (dddd,  $J = 10, 10, 10, 3$  Hz, 2H).

**Step 2:** Condensation of 6-(*trans*-4-[3-(3,4-difluorophenyl)propylamino]cyclohexyl)-3*H*-benzoxazol-2-one (400 mg, 1.0 mmol) with *p*-formaldehyde

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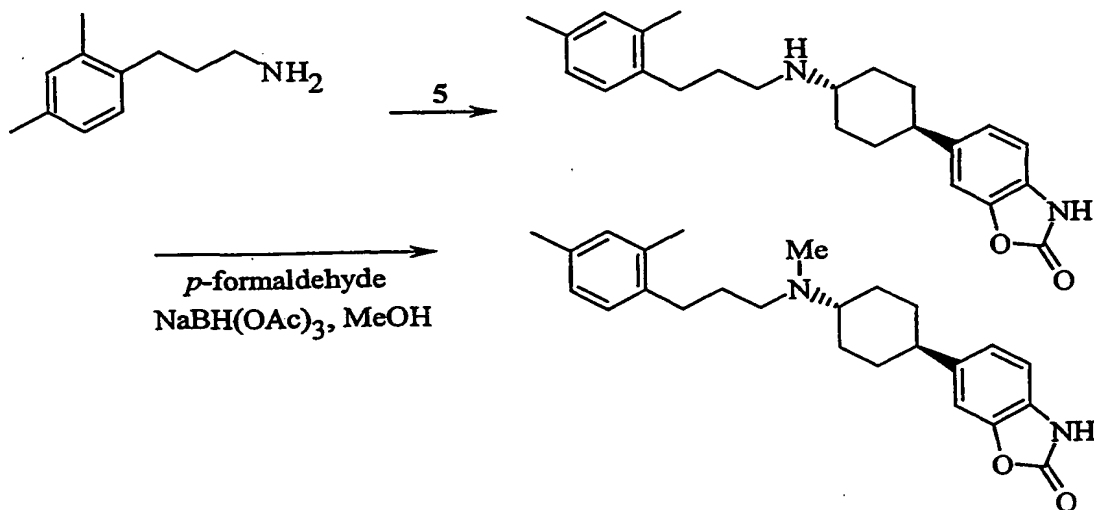
(740 mg, 24.7 mmol) following the procedure described in Example 17, except  $\text{CH}_2\text{Cl}_2$  (15 mL) was also added, followed by formation of the HCl salt, gave 6-(*trans*-4-{[3-(3,4-difluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one (226 mg, 52%), as a white solid: mp 224-227°C; IR (KBr):

2945, 1764  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  11.50 (s, 1H), 9.94 (s, 1H), 7.40-7.34 (m, 2H), 7.16 (s, 1H), 7.12-7.09 (m, 1H), 7.00 (s, 2H), 3.33-3.29 (m, 1H), 3.18-3.11 (m, 1H), 3.03-2.97 (m, 1H), 2.71 (d,  $J = 5$  Hz, 3H), 2.68-2.63 (m, 2H), 2.59-2.50 (m, 1H), 2.14-1.98 (m, 4H), 1.94-1.88 (m, 2H), 1.66-1.51 (m, 4H); ESI-MS ( $m/z$ ): 401  $[\text{M} + \text{H}]^+$ ; HPLC: method A, 5.97 minutes (97.1%); Anal. Calcd for  $\text{C}_{23}\text{H}_{26}\text{F}_2\text{N}_2\text{O}_2 \cdot \text{HCl}$ : C, 63.23; H, 6.23; N, 6.41. Found: C, 62.94; H, 6.56; N, 6.32.

## EXAMPLE 41

(a) 6-(*trans*-4-[3-(2,4-Dimethylphenyl)propylamino]cyclohexyl)-3*H*-benzoxazol-2-one

(b) 6-(*trans*-{4-[Methyl(2,4-dimethylphenylpropyl)amino]cyclohexyl})-3*H*-benzoxazol-2-one



Step 1: Coupling of 5 and 3-(2,4-dimethylphenyl)-1-propylamine, using the method given in Example 1, gave 6-(*trans*-4-[3-(2,4-dimethylphenyl)-propylamino]cyclohexyl)-3*H*-benzoxazol-2-one (684 mg, 41%):  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.12 (d,  $J = 1$  Hz, 1H), 7.01-6.88 (m, 5H), 3.50-3.20 (br

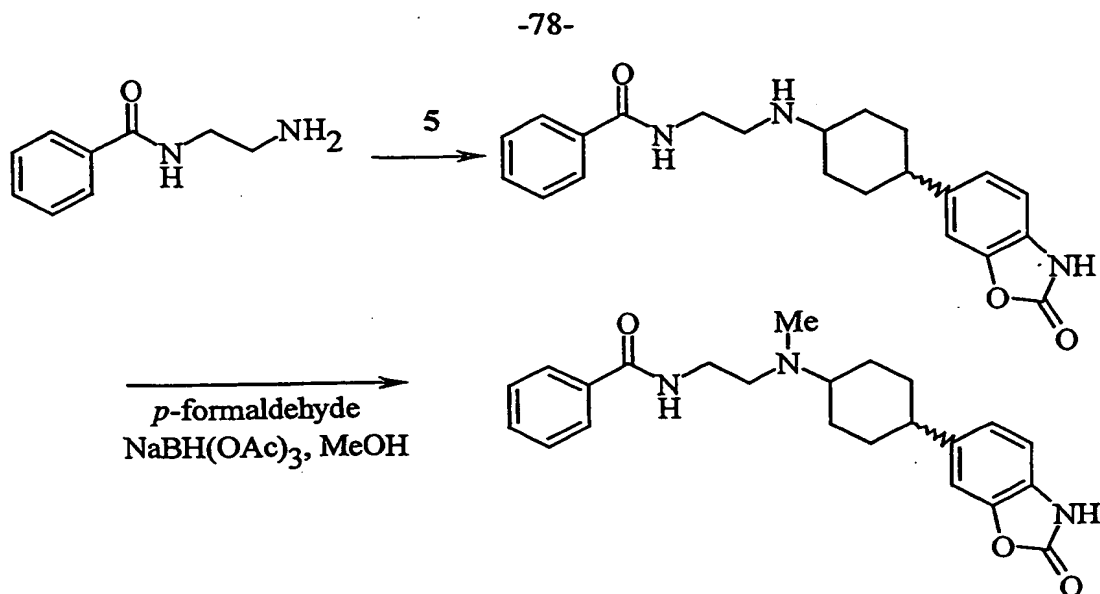
-77-

s, 2H), 2.59 (dd,  $J = 7, 7$  Hz, 2H), 2.55 (dd,  $J = 7, 7$  Hz, 2H), 2.49-2.39 (m, 2H), 2.22 (s, 3H), 2.21 (s, 3H), 1.98-1.92 (m, 2H), 1.81-1.75 (m, 2H), 1.65-1.59 (m, 2H), 1.44 (dddd,  $J = 10, 10, 10, 3$  Hz, 2H), 1.13 (dddd,  $J = 10, 10, 10, 3$  Hz, 2H).

5       Step 2: 6-(*trans*-4-[3-(2,4-Dimethylphenyl)propylamino]cyclohexyl)-3*H*-benzoxazol-2-one (400 mg, 1.0 mmol) was coupled with *p*-formaldehyde (740 mg, 24.7 mmol) following the procedure described in Example 17, except  $\text{CH}_2\text{Cl}_2$  (15 mL) was also added. Formation of the HCl salt gave 6-(*trans*-{4-[methyl(2,4-dimethylphenylpropyl)amino]cyclohexyl})-3*H*-benzoxazol-2-one (247 mg, 51%), as a white solid: mp 219-223°C; IR (KBr): 2944, 1770  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  11.51 (s, 1H), 10.14 (s, 1H), 7.17 (s, 1H), 7.06 (d,  $J = 8$  Hz, 1H), 7.00 (s, 2H), 6.98 (s, 1H), 6.94 (d,  $J = 8$  Hz, 1H), 3.35-3.30 (m, 1H), 3.22-3.15 (m, 1H), 3.09-3.01 (m, 1H), 2.70 (d,  $J = 5$  Hz, 3H), 2.61-2.52 (m, 3H), 2.25 (s, 3H), 2.23 (s, 3H), 2.16-2.07 (m, 2H), 1.98-1.87 (m, 4H), 1.68-1.51 (m, 4H); ESI-MS ( $m/z$ ): 393  $[\text{M} + \text{H}]^+$ ; HRMS-API ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{25}\text{H}_{32}\text{N}_2\text{O}_2$ , 393.2542; found, 393.2546; HPLC: method A, 6.40 minutes (99.4%); method B, 12.03 minutes (>99%); Anal. Calcd for  $\text{C}_{25}\text{H}_{32}\text{N}_2\text{O}_2 \cdot \text{HCl} \cdot 0.5\text{H}_2\text{O}$ : C, 68.55; H, 7.82; N, 6.40. Found: C, 68.32; H, 8.03; N, 6.74.

## EXAMPLE 42

- 20       (a) *N*-(2-{Methyl-[4-(2-oxo-2,3-dihydrobenzoxazol-6-yl)cyclohexyl]amino}-ethyl)benzamide
- (b) *N*-{2-[4-(2-Oxo-2,3-dihydrobenzoxazol-6-yl)cyclohexylamino]ethyl}-benzamide



**Step 1:** Coupling of ketone **5** and *N*-(2-aminoethyl)benzamide, using the method given in Example 1, followed by conversion to the HCl salt gave *N*-(2-{methyl-[4-(2-oxo-2,3-dihydrobenzoxazol-6-yl)cyclohexyl]amino}ethyl)-

benzamide (1.58 g, 58%) as a white solid (a mixture of *cis/trans* isomers):  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  8.84 (br s, 0.6H), 8.77 (br s, 1.4H), 7.92 (d,  $J = 7$  Hz, 2H), 7.56-7.48 (m, 3H), 7.34 (br s, 0.3H), 7.18 (s, 0.7H), 7.10 (d,  $J = 8$  Hz, 0.3H), 7.02-6.98 (m, 2.7H), 3.63-3.58 (m, 2H), 3.13-3.11 (m, 3H), 2.16 (m, 2H), 1.98-1.87 (m, 2H), 1.75-1.72 (m, 0.6H), 1.62-1.60 (m, 0.6H), 1.55-1.46 (m, 4.8H); ESI-MS ( $m/z$ ): 380  $[\text{M} + \text{H}]^+$ .

**Step 2:** Coupling of *N*-(2-{methyl-[4-(2-oxo-2,3-dihydrobenzoxazol-6-yl)cyclohexyl]amino}ethyl)benzamide (755 mg, 1.81 mmol) and *p*-formaldehyde (0.50 mL of a 37 wt% aqueous solution, 6.1 mmol), following the procedure described in Example 17 except NaOH (1.8 mL of a 1.0N aqueous solution, 1.8 mmol) and  $\text{CH}_2\text{Cl}_2$  (5 mL) were added, gave *N*-(2-[4-(2-oxo-2,3-dihydrobenzoxazol-6-yl)cyclohexylamino]ethyl)benzamide (528 mg, 66%), as a white solid (a mixture of *cis/trans* isomers): mp 167-175°C; IR (KBr): 2940, 1770, 1647  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO-}d_6$ ):  $\delta$  11.51 (s, 1H), 10.41 (br s, 0.7H), 10.03 (br s, 0.3H), 8.96-8.94 (m, 1H), 8.00-7.92 (m, 2H), 7.60-7.40 (m, 3H), 7.15 (s, 1H), 7.00 (s, 1H), 3.79-3.65 (m, 2H), 3.45-3.19 (m, 2H), 2.82-2.79 (m, 4H), 2.58-2.50 (m, 1H), 2.20-2.10 (m, 2H), 1.92-1.81 (m, 3H), 1.70-

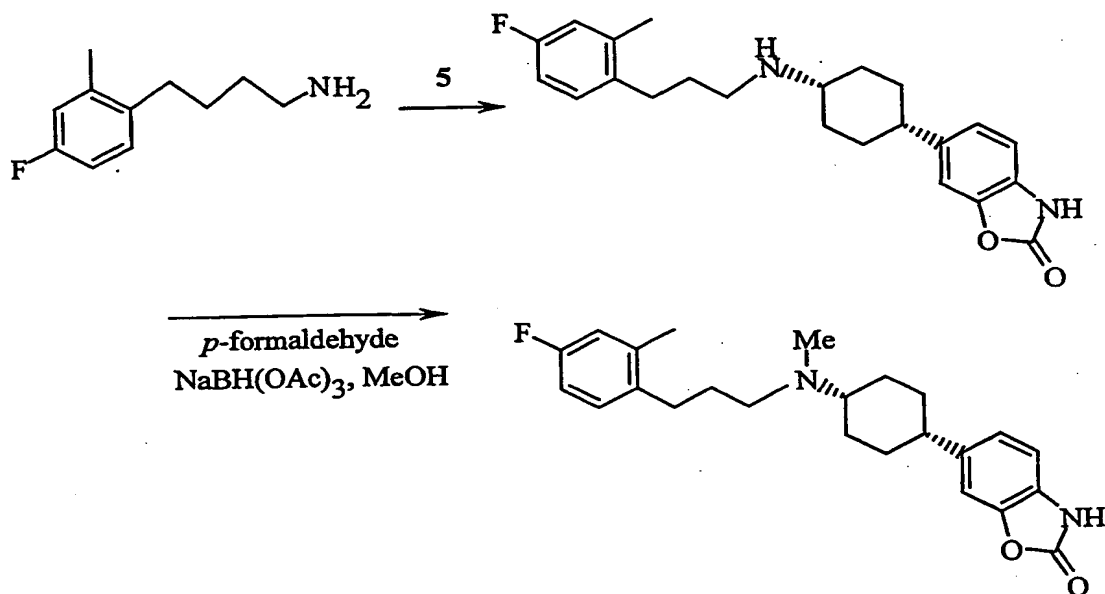
-79-

1.51 (m, 4H); ESI-MS ( $m/z$ ): 394  $[M + H]^+$ ; HPLC: method A, 4.89 minutes (95.0%); method B, 10.0 minutes (>99%); Anal. Calcd for  $C_{23}H_{27}FN_3O_3 \cdot HCl \cdot 0.75H_2O$ : C, 62.30; H, 6.71; N, 9.48. Found: C, 62.43; H, 6.68; N, 9.62.

5

## EXAMPLE 43

- (a) 6-(*trans*-4-[3-(4-Fluoro-2-methylphenyl)propylamino]cyclohexyl)-3*H*-benzoxazol-2-one; and  
 (b) 6-(*trans*-{4-[Methyl(4-fluoro-2-methylphenylpropyl)amino]cyclohexyl})-3*H*-benzoxazol-2-one



10

**Step 1:** Coupling of ketone 5 and 3-(4-fluoro-2-methylphenyl)-1-propylamine, using the method given in Example 1, gave 6-(*trans*-4-[3-(4-fluoro-2-methylphenyl)propylamino]cyclohexyl)-3*H*-benzoxazol-2-one (630 mg, 56%) as the HCl salt:  $^1H$  NMR (500 MHz,  $DMSO-d_6$ ):  $\delta$  11.50 (s, 1H), 8.88 (s, 2H), 7.22-7.13 (m, 2H), 7.05-6.91 (m, 4H), 3.09-2.87 (m, 3H), 2.67-2.62 (m, 3H), 2.30 (s, 3H), 2.17-2.13 (m, 2H), 1.92-1.79 (m, 4H), 1.58-1.41 (m, 4H).

15

**Step 2:** 6-(*trans*-4-[3-(4-Fluoro-2-methylphenyl)propylamino]cyclohexyl)-3*H*-benzoxazol-2-one (600 mg, 1.4 mmol) was coupled with *p*-formaldehyde (1.1 g, 37 mmol), following the procedure described in Example 17, gave 6-(*trans*-{4-[methyl(4-fluoro-2-methylphenylpropyl)amino]cyclohexyl})-3*H*-benzoxazol-2-one

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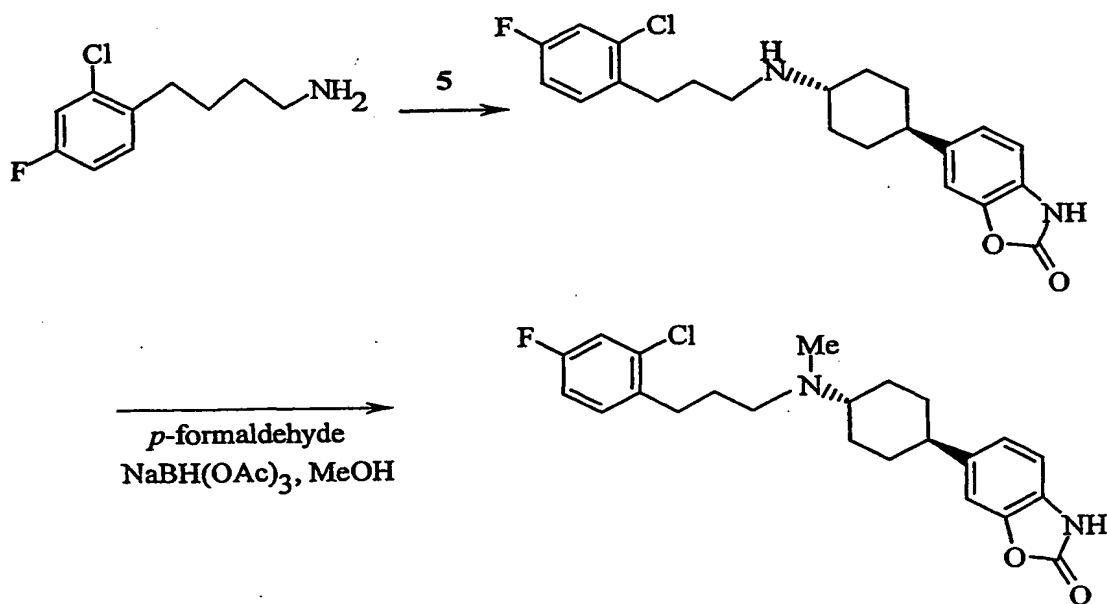
-80-

cyclohexyl}}-3*H*-benzoxazol-2-one (226 mg, 52%), as the HCl salt: mp 266-279°C; IR (KBr): 2950, 1768  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  11.50 (s, 1H), 10.20 (s, 1H), 7.24-7.20 (m, 1H), 7.17 (s, 1H), 7.04-6.94 (m, 4H), 3.32-3.30 (m, 1H), 3.21-3.02 (m, 2H), 3.15-3.02 (m, 1H), 2.70 (br s, 3H), 2.63-2.52 (m, 2H), 2.30 (s, 3H), 2.18-2.07 (m, 2H), 1.99-1.88 (m, 4H), 1.69-1.51 (m, 4H); ESI-MS ( $m/z$ ): 397  $[\text{M} + \text{H}]^+$ ; HRMS-API ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{24}\text{H}_{29}\text{FN}_2\text{O}_2$ , 397.2291; found, 397.2296; HPLC: method A, 5.99 minutes (99.0%); method B, 11.81 minutes (>99%); Anal. Calcd for  $\text{C}_{24}\text{H}_{29}\text{FN}_2\text{O}_2 \cdot \text{HCl} \cdot 0.25\text{H}_2\text{O}$ : C, 65.89; H, 7.03; N, 6.40. Found: C, 65.93; H, 7.10; N, 6.37.

10

## EXAMPLE 44

- (a) 6-{*trans*-4-[3-(2-Chloro-4-fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one; and  
 (b) 6-(*trans*-4-{[3-(2-Chloro-4-fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one



15

**Step 1:** Condensation of 3-(2-chloro-4-fluorophenyl)-1-propylamine (1.5 g, 6.5 mmol) and ketone 5 (1.5 g, 6.5 mmol), following the procedure described in Example 1, gave 6-{*trans*-4-[3-(2-chloro-4-fluorophenyl)-propylamino]cyclohexyl}-3*H*-benzoxazol-2-one (535 mg, 21%), as a white solid:

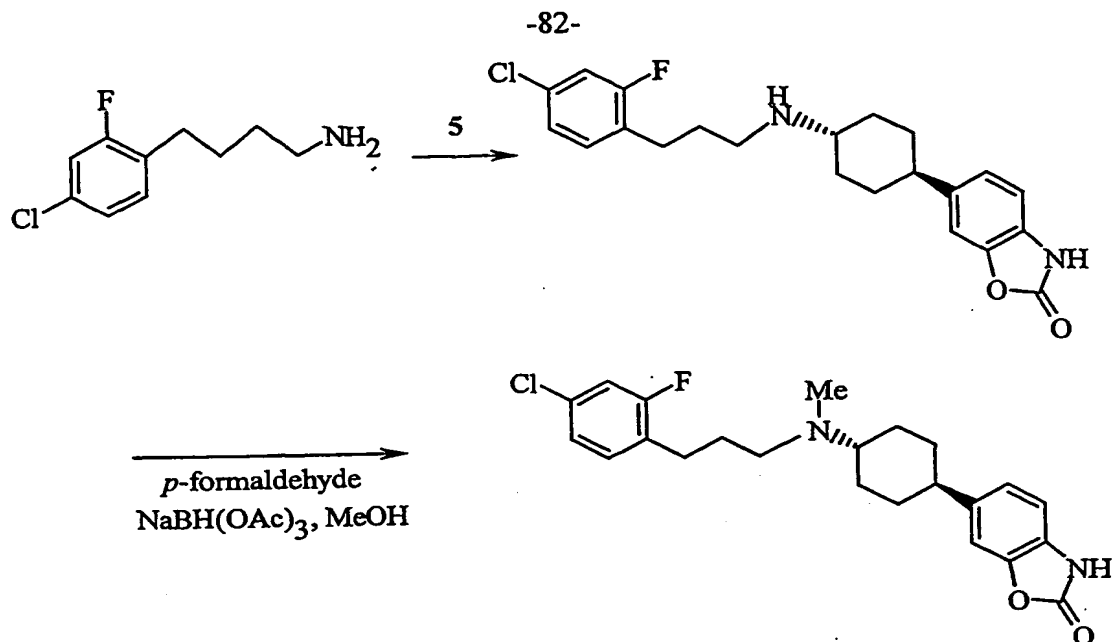
-81-

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 7.41-7.35 (m, 2H), 7.17-7.13 (m, 2H), 6.99-6.94 (m, 2H), 3.60-2.90 (br s, 2H), 2.72 (t, *J* = 8 Hz, 2H), 2.59 (t, *J* = 8 Hz, 2H), 2.49-2.40 (m, 2H), 1.95 (br d, *J* = 12 Hz, 2H), 1.77 (br d, *J* = 12 Hz, 2H), 1.69-1.66 (m, 2H), 1.44 (dddd, *J* = 13, 13, 13, 3 Hz, 2H), 1.13 (dddd, *J* = 13, 13, 13, 3 Hz, 2H).

Step 2: Condensation of 6-{*trans*-4-[3-(2-chloro-4-fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one (530 mg, 1.3 mmol) and *p*-formaldehyde (0.43 mL of a 37 wt% solution in H<sub>2</sub>O, 5.3 mmol), following the procedure described Example 17, followed by conversion to the HCl salt, gave 6-(*trans*-4-{[3-(2-chloro-4-fluorophenyl)propyl]methylamino}-cyclohexyl)-3*H*-benzoxazol-2-one (226 mg, 38%), as a white solid: mp 256-262°C; IR (KBr): 2948, 1770, 1492, 1451 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 11.49 (s, 1H), 10.05 (s, 1H), 7.49-7.42 (m, 2H), 7.24-7.19 (m, 1H), 7.17 (br s, 1H), 7.00 (d, *J* = 1 Hz, 2H), 3.35-3.29 (m, 1H), 3.24-3.18 (m, 1H), 3.11-3.03 (m, 1H), 2.84-2.70 (m, 5H), 2.59-2.51 (m, 1H), 2.18-1.88 (m, 6H), 1.69-1.51 (m, 4H); ESI (*m/z*): 417 [M + H]<sup>+</sup>; HRMS-API (*m/z*): [M + H]<sup>+</sup> calcd for C<sub>23</sub>H<sub>26</sub>ClFN<sub>2</sub>O<sub>2</sub>, 417.1745; found, 417.1748; HPLC: method A, 5.88 minutes (>99%); method B, 12.00 minutes (>99%); Anal. Calcd for C<sub>23</sub>H<sub>26</sub>ClFN<sub>2</sub>O<sub>2</sub>·HCl·0.25H<sub>2</sub>O: C, 60.33; H, 6.05; N, 6.12. Found: C, 60.35; H, 6.08; N, 5.93.

## EXAMPLE 45

- (a) 6-{*trans*-4-[3-(4-Chloro-2-fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one
- (b) 6-(*trans*-4-{[3-(4-Chloro-2-fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one



**Step 1:** Condensation of 3-(4-chloro-2-fluorophenyl)-1-propylamine (1.5 g, 6.5 mmol) and ketone 5 (1.5 g, 6.5 mmol), following the procedure described in Example 1, gave 6-{*trans*-4-[3-(4-chloro-2-fluorophenyl)-propylamino]cyclohexyl}-3*H*-benzoxazol-2-one (479 mg, 18%), as a white solid:

<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 7.36-7.32 (m, 2H), 7.22-7.20 (m, 1H), 7.13 (d, *J* = 1 Hz, 1H), 6.99-6.94 (m, 2H), 3.70-3.00 (br s, 2H), 2.64 (t, *J* = 8 Hz, 2H), 2.57 (t, *J* = 8 Hz, 2H), 2.47-2.38 (m, 2H), 1.94 (br d, *J* = 10 Hz, 2H), 1.77 (br d, *J* = 10 Hz, 2H), 1.70-1.64 (m, 2H), 1.44 (dddd, *J* = 13, 13, 13, 3 Hz, 2H), 1.13 (dddd, *J* = 13, 13, 13, 3 Hz, 2H).

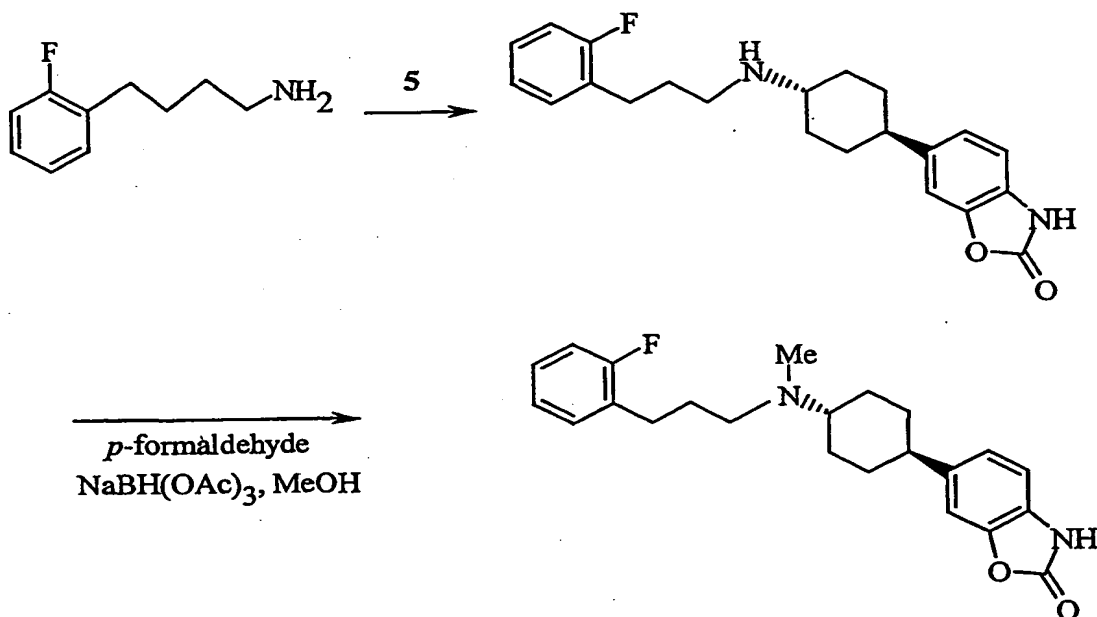
**Step 2:** Condensation of 6-{*trans*-4-[3-(4-chloro-2-fluorophenyl)-propylamino]cyclohexyl}-3*H*-benzoxazol-2-one (460 mg, 1.1 mmol) and *p*-formaldehyde (0.40 mL of a 37 wt% solution in H<sub>2</sub>O, 5.3 mmol), following the procedure described in Example 17 followed by conversion to the HCl salt, gave 6-{*trans*-4-[[3-(4-chloro-2-fluorophenyl)propyl]methylamino]cyclohexyl}-3*H*-benzoxazol-2-one (351 mg, 70%), as a white solid: mp 274-275 °C; IR (KBr): 2950, 1773, 1490, 1452 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 11.50 (s, 1H), 10.32 (s, 1H), 7.43-7.38 (m, 2H), 7.28-7.26 (m, 1H), 7.16 (br s, 1H), 7.00 (d, *J* = 1 Hz, 2H), 3.33-3.28 (m, 1H), 3.21-3.14 (m, 1H), 3.07-2.99 (m, 1H), 2.74-2.63 (m, 5H), 2.58-2.52 (m, 1H), 2.18-1.96 (m, 4H), 1.93-1.88 (m, 2H), 1.68-

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1.51 (m, 4H); ESI ( $m/z$ ): 417  $[M + H]^+$ ; HPLC: method A, 5.94 minutes (>99%); method B, 12.09 minutes (>99%); Anal. Calcd for  $C_{23}H_{26}ClFN_2O_2 \cdot HCl$ : C, 60.93; H, 6.00; N, 6.18. Found: C, 60.76; H, 6.09; N, 6.00.

## EXAMPLE 46

- 5 (a) 6-{*trans*-4-[3-(2-Fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one  
one  
(b) 6-(*trans*-4-{[3-(2-Fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-  
benzoxazol-2-one



- 10 Coupling of ketone 5 and 3-(2-fluorophenyl)-1-propylamine, using the  
method given in Example 1, gave 6-{*trans*-4-[3-(2-fluorophenyl)propylamino]-  
cyclohexyl}-3*H*-benzoxazol-2-one (1.7 g, 45%) as the HCl salt:  $^1H$  NMR  
(500 MHz, DMSO- $d_6$ ):  $\delta$  11.50 (s, 1H), 8.86 (s, 2H), 7.34 (t,  $J = 8$  Hz, 1H), 7.35-  
7.26 (m, 1H), 7.19-7.15 (m, 3H), 7.02-6.97 (m, 2H), 3.10-3.03 (m, 1H), 2.98-  
15 2.92 (m, 2H), 2.72 (dd,  $J = 8, 8$  Hz, 2H), 2.57-2.50 (m, 1H), 2.18-2.13 (m, 2H),  
1.98-1.92 (m, 2H), 1.89-1.85 (m, 2H), 1.57-1.46 (m, 4H).

6-{*trans*-4-[3-(2-Fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-  
2-one (700 mg, 1.7 mmol) was coupled with *p*-formaldehyde (0.37 g, 12.3 mmol),  
following the procedure described in Example 17, gave 6-(*trans*-4-{[3-(2-

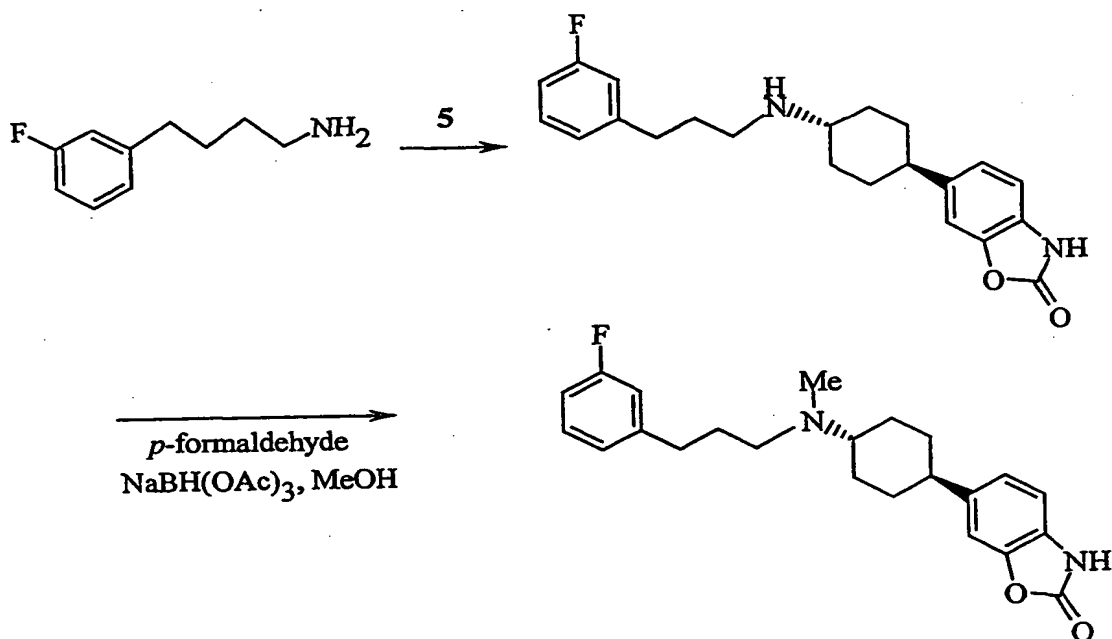
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fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one (407 mg, 57%), as the HCl salt: mp 242-246°C; IR (KBr): 2944, 1765 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 11.52 (s, 1H), 10.42 (s, 1H), 7.39-7.35 (m, 1H), 7.31-7.26 (m, 1H), 7.18-7.15 (m, 3H), 7.00 (s, 2H), 3.34-3.30 (m, 1H), 3.21-3.15 (m, 1H), 3.09-3.01 (m, 1H), 2.69 (d, *J* = 4 Hz, 5H), 2.58-2.51 (m, 1H), 2.18-1.98 (m, 4H), 1.93-1.87 (m, 2H), 1.69-1.51 (m, 4H); ESI-MS (*m/z*): 383 [M + H]<sup>+</sup>; HPLC: method A, 5.66 minutes (99.4%); method B, 11.21 minutes (>99%); Anal. Calcd for C<sub>23</sub>H<sub>27</sub>FN<sub>2</sub>O<sub>2</sub>·HCl·0.25H<sub>2</sub>O: C, 65.24; H, 6.78; N, 6.62. Found: C, 65.34; H, 6.65; N, 6.53.

## EXAMPLE 47

(a) 6-{*trans*-4-[3-(3-Fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one

(b) 6-(*trans*-4-{[3-(3-Fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one



Coupling of ketone 5 and 3-(3-fluorophenyl)-1-propylamine, using the method given in Example 1, gave 6-{*trans*-4-[3-(3-fluorophenyl)propylamino]-cyclohexyl}-3*H*-benzoxazol-2-one (1.4 g, 37%) as the HCl salt: <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 11.48 (s, 1H), 8.79 (s, 2H), 7.38-7.33 (m, 1H), 7.17 (s,

-85-

1H), 7.12-7.08 (m, 2H), 7.06-6.97 (m, 3H), 3.10-3.03 (m, 1H), 2.97-2.89 (m, 2H), 2.71 (dd,  $J = 8, 8$  Hz, 2H), 2.57-2.50 (m, 1H), 2.18-2.11 (m, 2H), 1.98-1.92 (m, 2H), 1.89-1.85 (m, 2H), 1.57-1.46 (m, 4H).

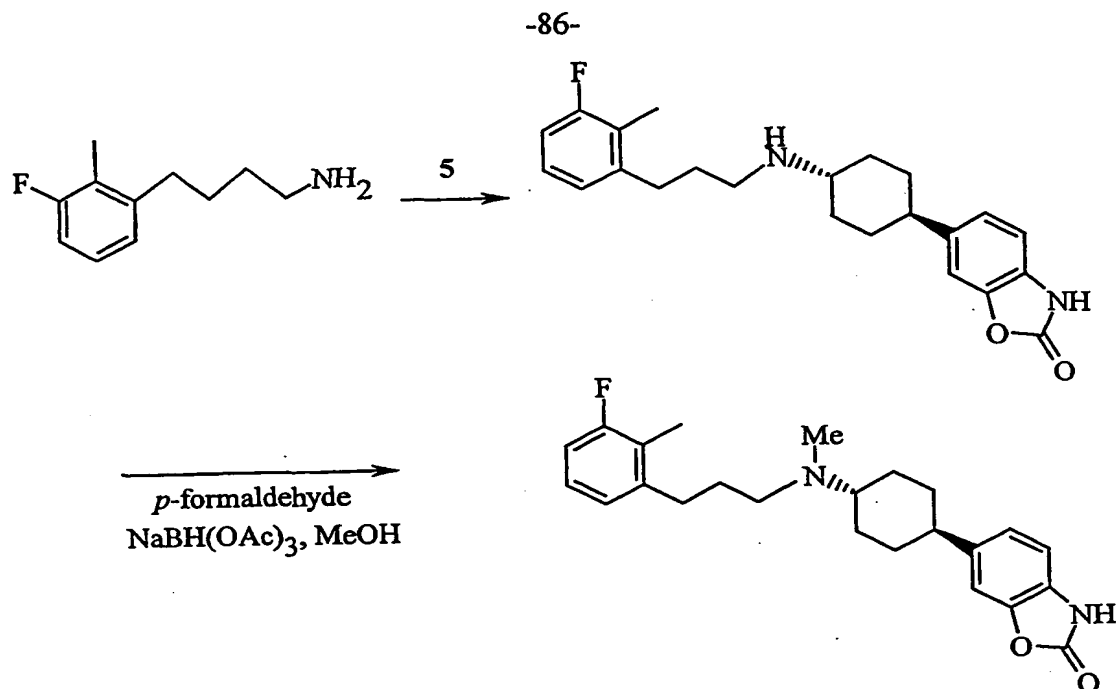
5 6-{*trans*-4-[3-(3-Fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one (700 mg, 1.7 mmol) was coupled with *p*-formaldehyde (0.37 g, 12.3 mmol), following the procedure described in Example 17, gave 6-(*trans*-4-{[3-(3-fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one (381 mg, 54%), as the HCl salt: mp 210-238°C; IR (KBr): 2944, 1763  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  11.51 (s, 1H), 10.21 (s, 1H), 7.38-7.34 (m, 1H), 7.16 (s, 10 1H), 7.14-7.09 (m, 2H), 7.04-7.02 (m, 1H), 7.00 (s, 2H), 3.33-3.30 (m, 1H), 3.19-3.11 (m, 1H), 3.05-2.98 (m, 1H), 2.72-2.63 (m, 5H), 2.58-2.51 (m, 1H), 2.18-1.98 (m, 4H), 1.93-1.87 (m, 2H), 1.69-1.51 (m, 4H); ESI-MS ( $m/z$ ): 383 [ $\text{M} + \text{H}$ ] $^+$ ; HPLC: method A, 5.75 minutes (99.0%); Anal. Calcd for  $\text{C}_{23}\text{H}_{27}\text{FN}_2\text{O}_2 \cdot \text{HCl}$ : C, 65.94; H, 6.74; N, 6.69. Found: C, 65.72; H, 6.77; N, 15 6.68.

## EXAMPLE 48

(a) 6-{*trans*-4-[3-(3-Fluoro-2-methylphenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one

(b) 6-(*trans*-4-{[3-(3-Fluoro-2-methylphenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one

20



Coupling of ketone 5 and 3-(2-methyl-3-fluorophenyl)-1-propylamine, using the method given in Example 1, gave 6-{*trans*-4-[3-(3-fluoro-2-methylphenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one (1.4 g, 56%): <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 7.16-7.10 (m, 2H), 7.01-6.93 (m, 4H), 2.65 (dd, *J* = 8, 8 Hz, 2H), 2.60 (dd, *J* = 7, 7 Hz, 2H), 2.49-2.39 (m, 2H), 2.18 (d, *J* = 2 Hz, 3H), 1.98-1.93 (m, 2H), 1.81-1.75 (m, 2H), 1.68-1.61 (m, 2H), 1.45 (dddd, *J* = 13, 13, 13, 3 Hz, 2H), 1.13 (dddd, *J* = 13, 13, 13, 3 Hz, 2H).

6-{*trans*-4-[3-(3-Fluoro-2-methylphenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one (700 mg, 1.7 mmol) was coupled with *p*-formaldehyde (1.48 g, 49.3 mmol), following the procedure described in Example 17, gave 6-(*trans*-4-[[3-(3-fluoro-2-methylphenyl)propyl]methylamino]cyclohexyl)-3*H*-benzoxazol-2-one (432mg, 55%), as the HCl salt: mp 264-269°C; IR (KBr): 2947, 1769 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 11.50 (s, 1H), 10.02 (s, 1H), 7.21-7.15 (m, 2H), 7.07-6.99 (m, 4H), 3.35-3.30 (m, 1H), 3.25-3.18 (m, 1H), 3.11-3.05 (m, 1H), 2.71 (d, *J* = 5 Hz, 3H), 2.70-2.62 (m, 2H), 2.58-2.51 (m, 1H), 2.20 (d, *J* = 2 Hz, 3H), 2.17-2.07 (m, 2H), 2.00-1.88 (m, 4H), 1.69-1.51 (m, 4H); ESI-MS (*m/z*): 397 [M + H]<sup>+</sup>; HPLC: method A, 6.09 minutes (98.3%); method B, 11.66 minutes

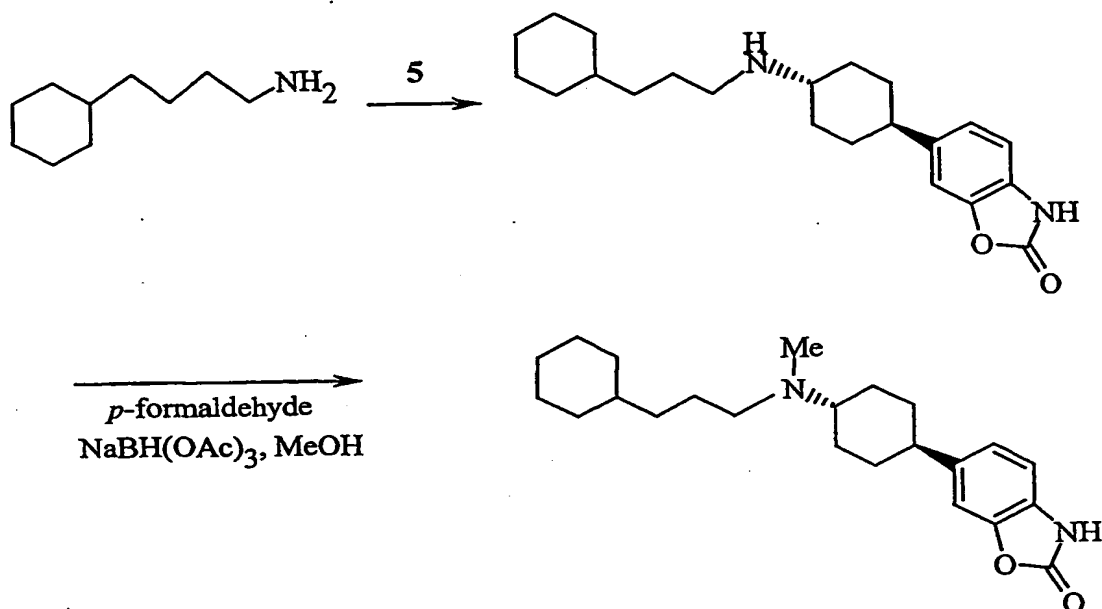
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(>99%); Anal. Calcd for  $C_{24}H_{29}FN_2O_2 \cdot HCl \cdot 0.25H_2O$ : C, 65.89; H, 7.03; N, 6.40. Found: C, 66.01; H, 6.85; N, 6.35.

## EXAMPLE 49

(a) 6-{*trans*-4-[(3-Cyclohexylpropyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one

5 (b) 6-{*trans*-4-[(3-Cyclohexylpropyl)methylamino]cyclohexyl}-3*H*-benzoxazol-2-one



**Step 1:** Condensation of cyclohexyl-1-propylamine (0.9 g, 6.4 mmol) and ketone 5 (1.5 g, 6.4 mmol), following the procedure described in Example 1, gave 6-{*trans*-4-[(3-cyclohexylpropyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one (352 mg, 15%), as a white solid:  $^1H$  NMR (500 MHz,  $DMSO-d_6$ ):  $\delta$  7.12 (br s, 1H), 6.97-6.93 (m, 2H), 3.70-3.10 (br s, 2H), 2.53 (t,  $J = 7$  Hz, 2H), 2.48-2.39 (m, 2H), 1.95 (br d,  $J = 12$  Hz, 2H), 1.77 (br d,  $J = 12$  Hz, 2H), 1.70-1.59 (m, 5H), 1.50-1.38 (m, 4H), 1.23-1.08 (m, 8H), 0.90-0.81 (m, 2H).

**Step 2:** Condensation of 6-{*trans*-4-[(3-cyclohexylpropyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one (350 mg, 0.98 mmol) and *p*-formaldehyde (0.40 mL of a 37 wt% solution in  $H_2O$ , 4.9 mmol), following the procedure described in Example 17 followed by conversion to the HCl salt, gave 6-{*trans*-4-[(3-cyclohexylpropyl)methylamino]cyclohexyl}-3*H*-benzoxazol-2-one (235 mg,



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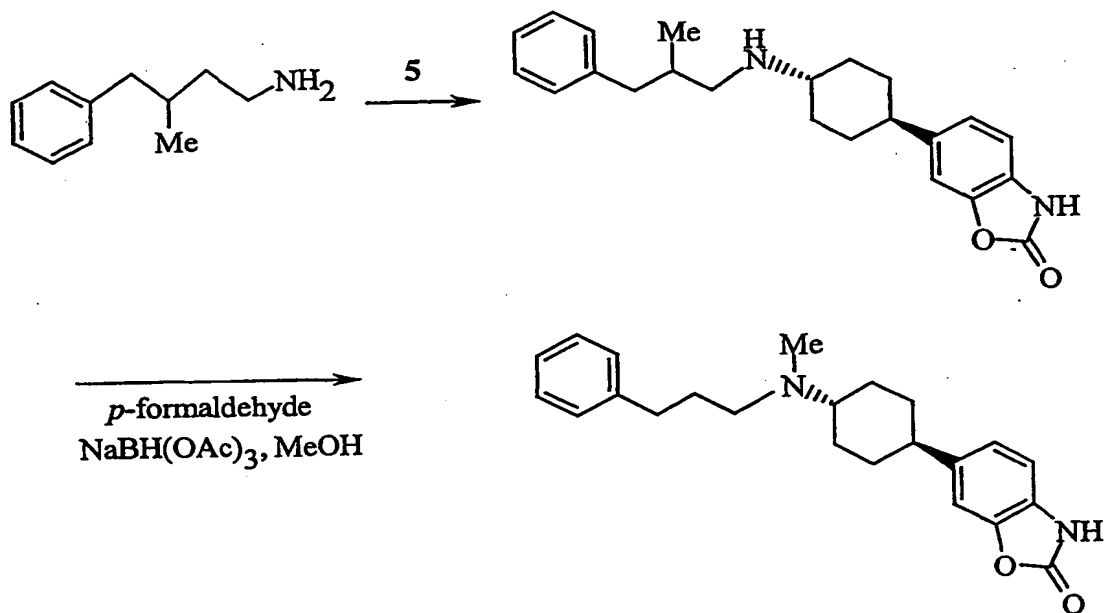
58%), as a white solid: mp 247-251°C; IR (KBr): 2931, 1771, 1502, 1451  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  11.50 (s, 1H), 10.12 (s, 1H), 7.16 (s, 1H), 7.00 (s, 2H), 3.32-3.25 (m, 1H), 3.11-3.04 (m, 1H), 2.99-2.91 (m, 1H), 2.67 (d,  $J = 5$  Hz, 3H), 2.59-2.52 (m, 1H), 2.18-2.08 (m, 2H), 1.94-1.88 (m, 2H), 1.76-1.51 (m, 11 H), 1.29-1.09 (m, 6H), 0.93-0.85 (m, 2H); ESI ( $m/z$ ): 371  $[\text{M} + \text{H}]^+$ ; HRMS-API ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{23}\text{H}_{34}\text{N}_2\text{O}_2$ , 371.2698; found, 371.2708; HPLC: method A, 6.32 minutes (99.0%); method B, 12.58 minutes (>99%); Anal. Calcd for  $\text{C}_{23}\text{H}_{34}\text{N}_2\text{O}_2 \cdot \text{HCl} \cdot 0.25\text{H}_2\text{O}$ : C, 67.13; H, 8.70; N, 6.81. Found: C, 67.24; H, 8.65; N, 6.73.

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## EXAMPLE 50

(a) 6-{*trans*-[4-(2-Methyl-3-phenylpropylamino)cyclohexyl]}-3*H*-benzoxazol-2-one

(b) 6-(*trans*-{4-[Methyl(2-methyl-3-phenylpropyl)amino]cyclohexyl})-3*H*-benzoxazol-2-one



15

**Step 1:** Condensation of 2-methyl-3-phenylpropylamine (830 mg, 3.97 mmol) and ketone 5 (918 mg, 3.97 mmol), following the procedure described in Example 1, gave compound 6-{*trans*-[4-(2-methyl-3-phenylpropylamino)-cyclohexyl]}-3*H*-benzoxazol-2-one (400 mg, 48%):  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-$

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$d_6$ ):  $\delta$  7.32-7.21 (m, 2H), 7.19-7.17 (m, 4H), 7.03-6.98 (m, 2H), 2.77 (dd,  $J = 13$ , 6 Hz, 1H), 2.55-2.34 (m, 7H), 1.99-1.97 (m, 2H), 1.84-1.80 (m, 2H), 1.50-1.47 (m, 2H), 1.18-1.05 (m, 2H), 0.88 (d,  $J = 6$  Hz, 3H).

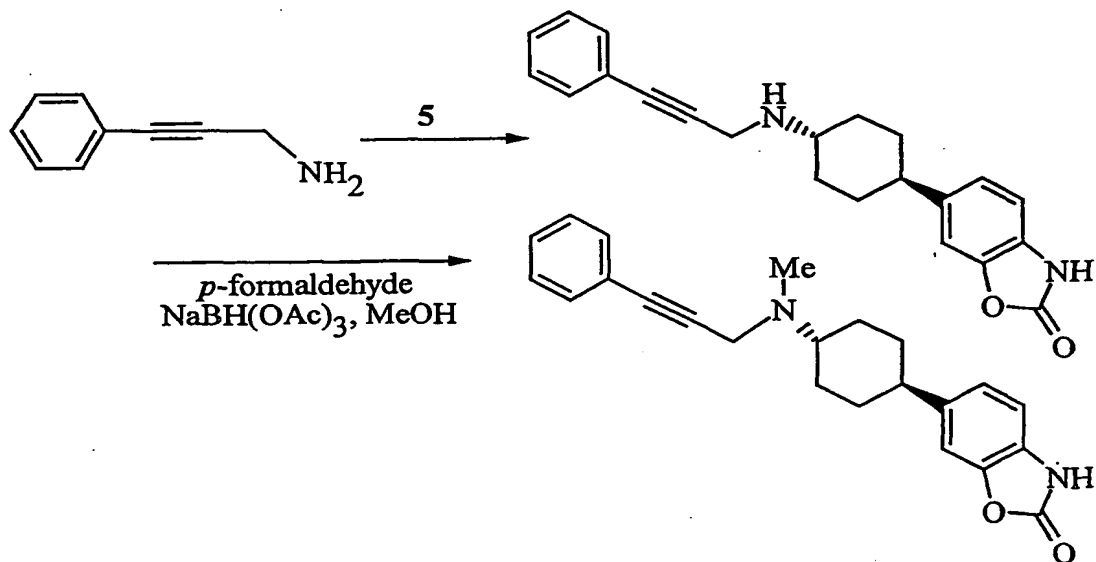
**Step 2:** Condensation of 6-{*trans*-[4-(2-methyl-3-phenylpropylamino)-cyclohexyl]}-3*H*-benzoxazol-2-one (400 mg, 1.10 mmol) and *p*-formaldehyde (0.50 mL of a 37 wt% solution in H<sub>2</sub>O, 2.4 mmol), following the procedure described in Example 17, gave 6-(*trans*-{4-[methyl(2-methyl-3-phenylpropyl)-amino]cyclohexyl})-3*H*-benzoxazol-2-one (200 mg, 52%), as a white foam:

mp 43-48°C; IR (film): 2927, 1776, 1495, 1450 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO- $d_6$ ):  $\delta$  7.28-7.25 (m, 2H), 7.17-7.15 (m, 4H), 7.00-6.95 (m, 2H), 2.78 (dd,  $J = 13$ , 5 Hz, 1H), 2.46-2.41 (m, 1H), 2.29-2.14 (m, 6H), 1.83-1.78 (m, 6H), 1.49-1.34 (m, 4H), 0.76 (d,  $J = 6$  Hz, 3H); ESI ( $m/z$ ): 379 [M + H]<sup>+</sup>; HPLC: method A, 5.96 minutes (>99%); method B, 10.99 minutes (97.1%); Anal. Calcd for C<sub>24</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>·0.125H<sub>2</sub>O: C, 75.51; H, 8.25; N, 7.34. Found: C, 75.26; H, 7.88; N, 7.20.

## EXAMPLE 51

(a) 6-{*trans*-[4-(3-Phenyl-prop-2-ynylamino)cyclohexyl]}-3*H*-benzoxazol-2-one

(b) 6-(*trans*-{4-[Methyl(3-phenyl-prop-2-ynyl)amino]cyclohexyl})-3*H*-benzoxazol-2-one



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**Step 1:** Condensation of 3-phenyl-prop-2-ynylamine (1.0 g, 7.6 mmol) and ketone 5 (1.7 g, 7.6 mmol), following the procedure described in Example 1, except THF was used as solvent gave compound 6-{*trans*-[4-(3-phenyl-prop-2-ynylamino)cyclohexyl]}-3*H*-benzoxazol-2-one (400 mg, 58%) as a white solid:

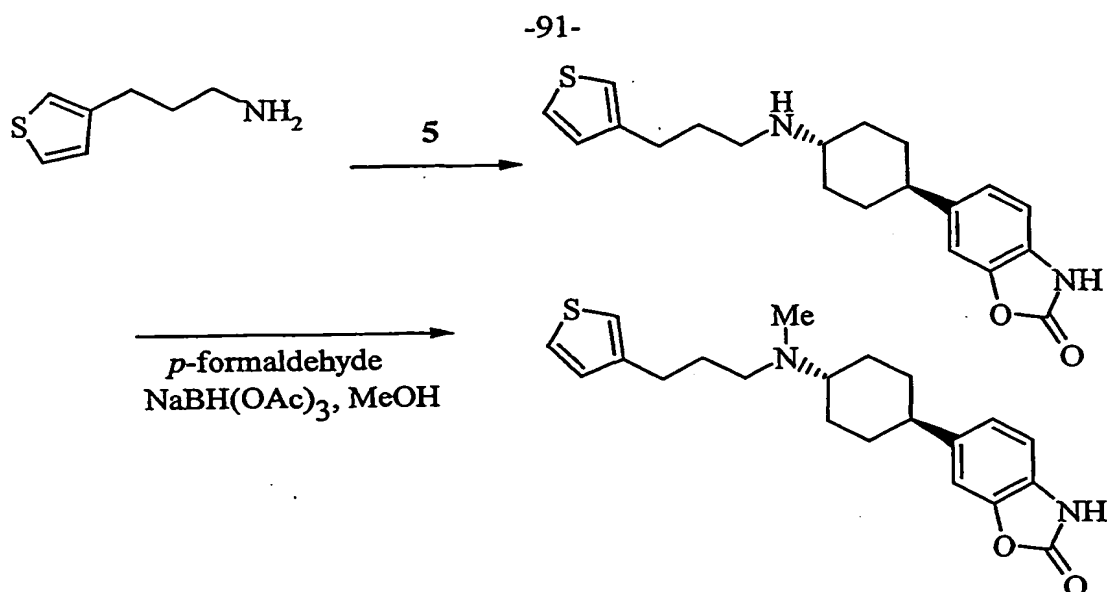
<sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 7.45-7.35 (m, 5H), 7.19 (s, 1H), 7.50-6.94 (m, 2H), 3.59 (s, 2H), 3.30 (m, 2H), 2.75-2.61 (m, 1H), 2.06-2.00 (m, 2H), 1.85-1.80 (m, 2H), 1.58-1.41 (m, 2H), 1.25-1.10 (m, 2H).

**Step 2:** Condensation of 6-{*trans*-[4-(3-phenyl-prop-2-ynylamino)-cyclohexyl]}-3*H*-benzoxazol-2-one (400 mg, 1.20 mmol) and *p*-formaldehyde (180 mg of a 37 wt% solution in H<sub>2</sub>O, 6.0 mmol), following the procedure described in Example 17, gave 6-(*trans*-{4-[methyl(3-phenyl-prop-2-ynyl)-amino]cyclohexyl})-3*H*-benzoxazol-2-one (100 mg, 65%), as a white solid: mp 249-252°C; IR (KBr): 2938, 2627, 1770 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 7.55 (d, *J* = 6 Hz, 2H), 7.47-7.43 (m, 2H), 7.20 (s, 1H), 7.03-6.98 (m, 2H), 4.38 (s, 2H), 3.42-3.33 (m, 3H), 2.86 (s, 3H), 2.56-2.50 (m, 1H), 2.22 (m, 2H), 1.94 (brd, *J* = 11 Hz, 2H), 1.71-1.67 (m, 2H), 1.57-1.55 (m, 2H); HRMS-APCI (*m/z*): [M + H]<sup>+</sup> calcd for C<sub>23</sub>H<sub>25</sub>N<sub>2</sub>O<sub>2</sub>, 361.1916; found, 361.1914; HPLC: method A, 5.74 minutes (>99%); method B, 11.03 minutes (>99%); Anal. Calcd for C<sub>23</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>·HCl·0.5H<sub>2</sub>O: C, 68.06; H, 6.46; N, 6.90. Found: C, 67.81; H, 6.65; N, 6.74.

#### EXAMPLE 52

(a) 6-{*trans*-4-[4-(3-Thiophen-3-yl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one

(b) 6-[*trans*-4-{[3-(3-Thiophen-3-yl)propyl]methylamino}cyclohexyl]-3*H*-benzoxazol-2-one



**Step 1:** Condensation of (3-thienyl)-1-propylamine (2.8 g, 20.0 mmol) and ketone 5 (4.6 g, 20.0 mmol), following the procedure described in Example 1, gave compound 6-*{trans-4-[4-(3-thiophen-3-yl)propylamino]cyclohexyl}*-3*H*-benzoxazol-2-one (410 mg, 5%), as a white solid:  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ ):  $\delta$  7.43-7.41 (m, 1H), 7.14-7.12 (m, 2H), 7.00-6.93 (m, 3H), 3.60-3.10 (br s, 2H), 2.63 (t,  $J = 7$  Hz, 2H), 2.58 (t,  $J = 7$  Hz, 2H), 2.49-2.39 (m, 2H), 1.95 (br d,  $J = 11$  Hz, 2H), 1.78 (br d,  $J = 11$  Hz, 2H), 1.73-1.68 (m, 2H), 1.45 (dddd,  $J = 13, 13, 13, 3$  Hz, 2H), 1.13 (dddd,  $J = 13, 13, 13, 3$  Hz, 2H).

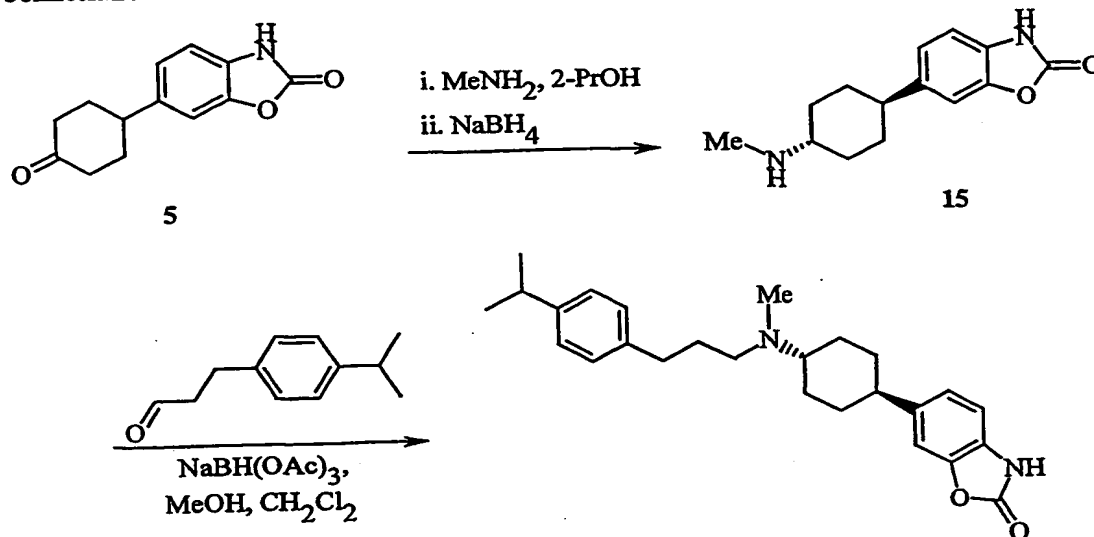
**Step 2:** Condensation of 6-*{trans-4-[4-(3-thiophen-3-yl)propylamino]cyclohexyl}*-3*H*-benzoxazol-2-one (400 mg, 1.0 mmol) and *p*-formaldehyde (0.17 mL of a 37 wt% solution in  $\text{H}_2\text{O}$ , 2.0 mmol), following the procedure described in Example 17, followed by conversion to the HCl salt, gave 6-*[trans-4-[[3-(3-thiophen-3-yl)propyl]methylamino]cyclohexyl]*-3*H*-benzoxazol-2-one (301 mg, 74%), as a white solid: mp 246-248°C; IR (KBr): 2950, 1759, 1496, 1451  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz, DMSO- $d_6$ ):  $\delta$  11.47 (s, 1H), 10.09 (s, 1H), 7.50-7.48 (m, 1H), 7.25-7.24 (m, 1H), 7.16 (s, 1H), 7.05-7.04 (m, 1H), 7.00 (s, 2H), 3.34-3.28 (m, 1H), 3.19-3.10 (m, 1H), 3.05-2.98 (m, 1H), 2.71 (d,  $J = 5$  Hz, 3H), 2.69-2.65 (m, 2H), 2.58-2.51 (m, 1H), 2.15-2.00 (m, 4H), 1.94-1.88 (m, 2H), 1.68-1.51 (m, 4H); ESI ( $m/z$ ): 371  $[\text{M} + \text{H}]^+$ ; HPLC: method B, 10.79 minutes (>99%);

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Anal. Calcd for  $C_{21}H_{26}N_2O_2S \cdot HCl$ : C, 61.98; H, 6.69; N, 6.88. Found: C, 61.64; H, 6.79; N, 6.70.

## EXAMPLE 53

6-(*trans*-4-[[3-(4-Isopropylphenyl)propyl]methylamino]cyclohexyl)-3*H*-benzoxazol-2-one



**Step 1:** To a suspension of ketone 5 (10.4 g, 0.045 mol) in 2-PrOH (520 mL) was added methylamine (33.7 mL of a 2.0 M solution in THF, 0.067 mol). A clear, amber solution formed after ca 15 minutes, and a precipitate gradually formed a few minutes later. After 1.5 hours, the reaction mixture was cooled in an ice/water bath, NaBH<sub>4</sub> (2.6 g, 0.067 mol) was added, and stirring was continued at 0°C for 35 minutes. The reaction mixture was stirred at room temperature for 15 hours. MeOH (ca 2 mL) was added to quench any excess NaBH<sub>4</sub> (no gas evolution was observed), and the solvents were removed under reduced pressure. The residue was partitioned between 1N HCl (500 mL) and EtOAc (250 mL). The aqueous layer was separated, adjusted to pH 7-8 with solid NaHCO<sub>3</sub>, and washed with EtOAc (200 mL). A precipitate formed during the wash, which was collected by vacuum filtration and dried to give 6-[*trans*-4-(methylamino)cyclohexyl]-3*H*-benzoxazol-2-one 15 (5.0 g, 46%). The organic layer was separated, and TLC analysis (89:10:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH) showed it contained compound 15. Compound 15 was also shown by TLC analysis to be

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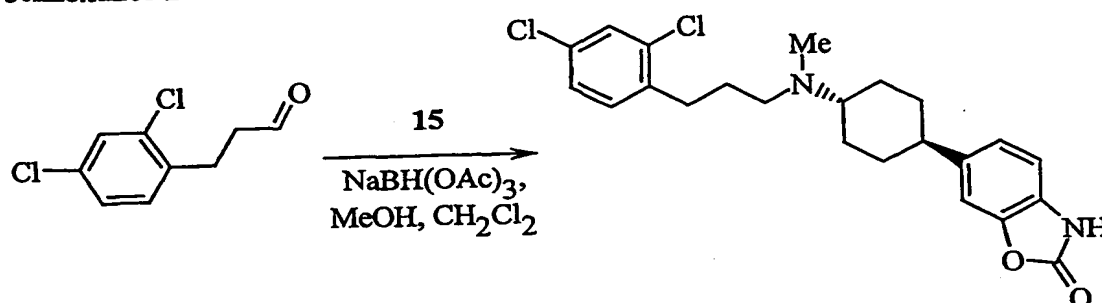
present in the initial EtOAc extraction. The organic extracts were combined, concentrated under reduced pressure, dissolved in a minimal amount of MeOH, and a solid was precipitated out with diethyl ether. The solid was collected by vacuum filtration and dried to give **15** (1.6 g, 13%) as the HCl salt. To the aqueous layer (ca 1L), which also showed the presence of additional **15** by TLC, was added solid NaCl (ca 80 g), and the solution was concentrated under reduced pressure to approximately half its original volume. A solid formed and was collected by vacuum filtration and dried to give **15** (1.3 g, 12%). The solids were combined to give 6-[*trans*-4-(methylamino)cyclohexyl]-3*H*-benzoxazol-2-one **15** (7.9 g, 73%): <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD): δ 7.10 (d, *J* = 1.5 Hz, 1H), 7.03 (dd, *J* = 8, 1.5 Hz, 1H), 6.98 (d, *J* = 8 Hz, 1H), 2.67-2.52 (m, 2H), 2.49 (s, 3H), 2.15-2.12 (m, 2H), 1.97-1.94 (m, 2H), 1.61-1.52 (m, 2H), 1.38-1.30 (m, 2H).

**Step 2:** To a solution of amine **15** (670 mg, 2.40 mmol) in 1:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH (30 mL) was added solid NaHCO<sub>3</sub> (200 mg, 2.40 mmol) and, after 10 minutes, 3-(4-isopropylphenyl)propionaldehyde (420 mg, 2.40 mmol). After stirring for 5 minutes, NaBH(OAc)<sub>3</sub> (760 mg, 3.60 mmol) was added, and the mixture was stirred at room temperature for 12 hours. The reaction mixture was brought to pH 8 with solid NaOH and concentrated under reduced pressure. Purification by flash chromatography (silica, 95:5 CH<sub>2</sub>Cl<sub>2</sub>:MeOH followed by 89:10:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH), followed by formation of the HCl salt and recrystallization (MeOH:Et<sub>2</sub>O) gave 6-(*trans*-4-{[3-(4-isopropylphenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one (514 mg, 48%), as a white solid: mp 179-181°C; IR (KBr): 2959, 1771, 1498, 1451 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 11.48 (s, 1H), 10.10 (s, 1H), 7.17-7.15 (m, 5H), 7.00 (br s, 2H), 3.32-3.29 (m, 1H), 3.19-3.11 (m, 1H), 3.06-2.99 (m, 1H), 2.89-2.83 (m, 1H), 2.70 (d, *J* = 4 Hz, 3H), 2.63-2.52 (m, 3H), 2.15-1.95 (m, 4H), 1.93-1.87 (m, 2H), 1.66-1.50 (m, 4H), 1.19 (d, *J* = 7 Hz, 6H); ESI (*m/z*): 407 [M + H]<sup>+</sup>; method B, 12.69 minutes (>99%); Anal. Calcd for C<sub>26</sub>H<sub>34</sub>N<sub>2</sub>O<sub>2</sub>·HCl: C, 70.49; H, 7.96; N, 6.32. Found: C, 70.29; H, 8.05; N, 6.28.

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## EXAMPLE 54

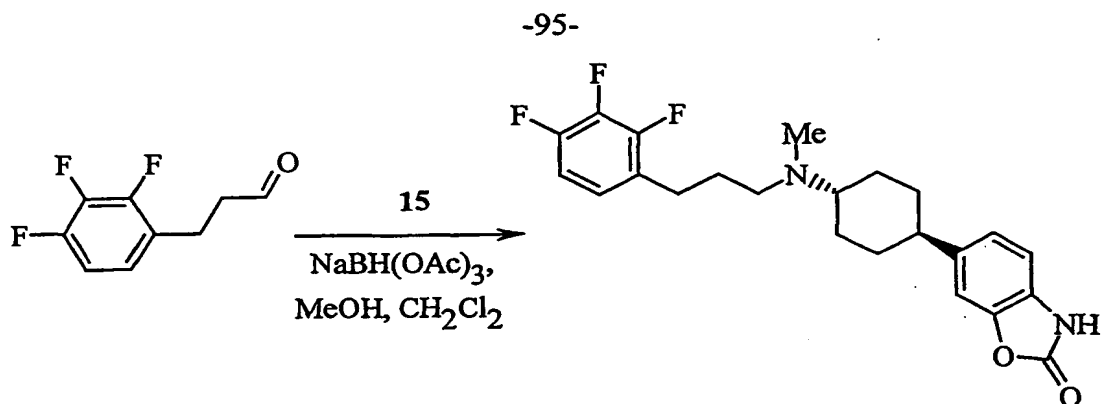
6-(*trans*-4-{{3-(2,4-Dichlorophenyl)propyl}methylamino}cyclohexyl)-3*H*-benzoxazol-2-one



- 5            Condensation of 15 (550 mg, 1.9 mmol) and 3-(2,4-dichlorophenyl)-propionaldehyde (390 mg, 1.9 mmol) following the procedure described in Example 45, Step 2, followed by conversion to the HCl salt, gave 6-(*trans*-4-{{3-(2,4-dichlorophenyl)propyl}methylamino}cyclohexyl)-3*H*-benzoxazol-2-one (446 mg, 50%), as an off-white solid: mp 273-279°C; IR (KBr): 2949, 1775, 1500, 1474 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 11.49 (s, 1H), 10.01 (s, 1H), 7.61 (d, *J* = 2 Hz, 1H), 7.47-7.41 (m, 2H), 7.17 (s, 1H), 7.00 (s, 2H), 3.34-3.29 (m, 1H), 3.22-3.17 (m, 1H), 3.11-3.03 (m, 1H), 2.79-2.73 (m, 2H), 2.71 (d, *J* = 5 Hz, 3H), 2.59-2.48 (m, 1H), 2.14-2.06 (m, 2H), 2.03-1.97 (m, 2H), 1.94-1.88 (m, 2H), 1.69-1.50 (m, 4H); ESI (*m/z*): 433 [M + H]<sup>+</sup>; HPLC: method A, 6.78 minutes (>99%); Anal. Calcd for C<sub>23</sub>H<sub>26</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub>·HCl: C, 58.80; H, 5.79; N, 5.96.
- 10
- 15            Found: C, 58.62; H, 5.76; N, 5.89.

## EXAMPLE 55

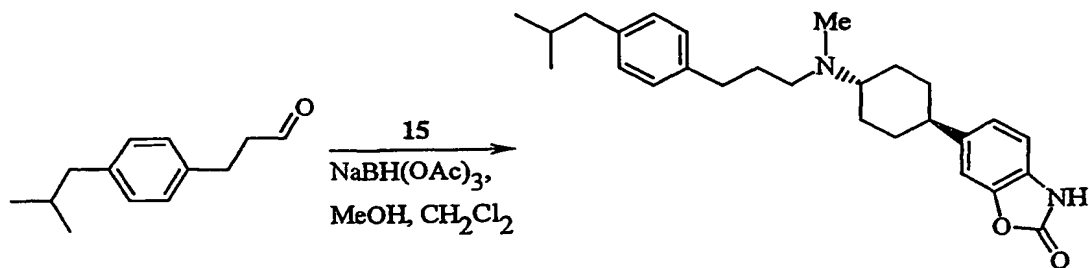
6-(*trans*-4-{{3-(2,3,4-Trifluorophenyl)propyl}methylamino}cyclohexyl)-3*H*-benzoxazol-2-one



Condensation of 15 (420 mg, 1.5 mmol) and 3-(2,3,4-trifluorophenyl)-propionaldehyde (280 mg, 1.5 mmol), following the procedure described in Example 45, Step 2, followed by conversion to the HCl salt, gave 6-(*trans*-4-([3-(2,3,4-trifluorophenyl)propyl]methylamino)cyclohexyl)-3*H*-benzoxazol-2-one (257 mg, 33%), as an off-white solid: mp 269-274°C; IR (KBr): 2950, 1768, 1513, 1485  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  11.50 (s, 1H), 10.17 (s, 1H), 7.23-7.21 (m, 2H), 7.17 (br s, 1H), 7.00 (d,  $J = 1$  Hz, 2H), 3.33-3.26 (m, 1H), 3.21-3.14 (m, 1H), 3.08-3.01 (m, 1H), 2.79-2.71 (m, 2H), 2.69 (d,  $J = 5$  Hz, 3H), 2.59-2.50 (m, 1H), 2.16-1.98 (m, 4H), 1.94-1.87 (m, 2H), 1.68-1.50 (m, 4H); HRMS-APCI ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{23}\text{H}_{25}\text{F}_3\text{N}_2\text{O}_2$ , 419.1946; found, 419.1948; HPLC: method A, 8.31 minutes (97.7%); method B, 11.85 minutes (97.8%); Anal. Calcd for  $\text{C}_{23}\text{H}_{25}\text{F}_3\text{N}_2\text{O}_2 \cdot \text{HCl} \cdot 0.25\text{H}_2\text{O}$ : C, 60.13; H, 5.81; N, 6.10. Found: C, 60.14; H, 5.70; N, 6.08.

#### EXAMPLE 56

6-(*trans*-4-([3-(4-isobutylphenyl)propyl]methylamino)cyclohexyl)-3*H*-benzoxazol-2-one



Condensation of 15 (1.0 g, 3.6 mmol) and 3-(4-isobutylphenyl)-propionaldehyde (700 mg, 3.6 mmol), following the procedure described in

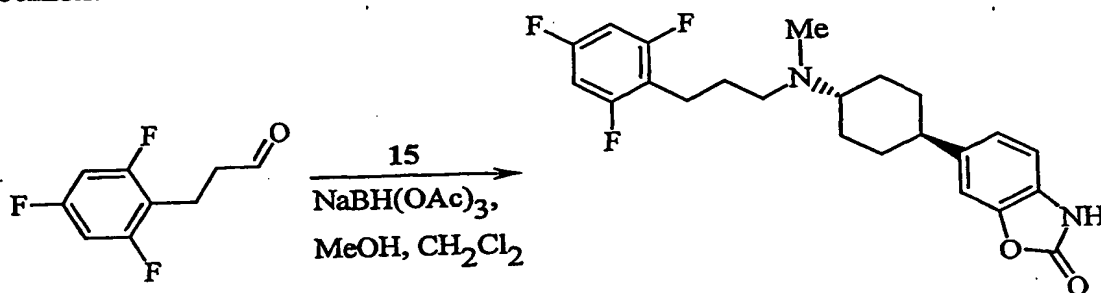


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Example 45, Step 2, followed by conversion to the HCl salt, gave 6-(*trans*-4-{[3-(4-isobutylphenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one (977 mg, 61%), as an off-white solid: mp 162-165°C; IR (KBr): 2953, 1773, 1498, 1451  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  11.55 (s, 1H), 10.00 (s, 1H), 7.17-7.08 (m, 5H), 7.00 (s, 2H), 3.32-3.28 (m, 1H), 3.21-3.08 (m, 1H), 3.08-2.95 (m, 1H), 2.70 (d,  $J = 5$  Hz, 3H), 2.65-2.52 (m, 3H), 2.41 (d,  $J = 7$  Hz, 2H), 2.14-1.73 (m, 7H), 1.68-1.49 (m, 4H), 0.85 (d,  $J = 7$  Hz, 6H); HRMS-API ( $m/z$ ):  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{27}\text{H}_{36}\text{N}_2\text{O}_2$ , 421.2855; found, 421.2858; HPLC: method A, 7.49 minutes (>99%); method B, 13.59 minutes (>99%); Anal. Calcd for  $\text{C}_{27}\text{H}_{36}\text{N}_2\text{O}_2 \cdot \text{HCl} \cdot 0.5\text{H}_2\text{O}$ : C, 69.58; H, 8.22; N, 6.01. Found: C, 69.23; H, 8.20; N, 5.87.

## EXAMPLE 57

6-(*trans*-4-{[3-(2,4,6-Trifluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one



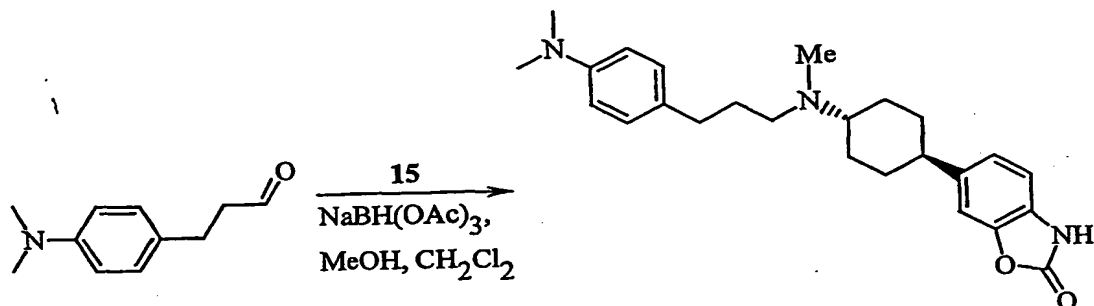
Condensation of 15 (460 mg, 1.9 mmol) and 3-(2,4,6-trifluorophenyl)propionaldehyde (360 mg, 1.9 mmol), following the procedure described in Example 45, Step 2, followed by conversion to the HCl salt, gave 6-(*trans*-4-{[3-(2,4,6-trifluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one (275 mg, 32%), as a white solid: mp 235-238°C; IR (KBr): 2949, 1772, 1632, 1603  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  11.54 (s, 1H), 9.78 (s, 1H), 7.26-7.18 (m, 3H), 7.00 (s, 2H), 3.32-3.27 (m, 1H), 3.26-3.04 (m, 2H), 2.71 (d,  $J = 5$  Hz, 3H), 2.58-2.54 (m, 1H), 2.66-2.62 (m, 2H), 2.12-1.86 (m, 6H), 1.68-1.48 (m, 4H); ESI ( $m/z$ ): 419  $[\text{M} + \text{H}]^+$ ; HPLC: method A, 6.30 minutes (98.8%);

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Anal. Calcd for  $C_{23}H_{25}F_3N_2O_2 \cdot HCl$ : C, 60.73; H, 5.76; N, 6.16. Found: C, 60.43; H, 5.71; N, 5.99.

## EXAMPLE 58

6-(4-{{3-(*trans*-4-Dimethylaminophenyl)propyl}methylamino}cyclohexyl)-3*H*-benzoxazol-2-one

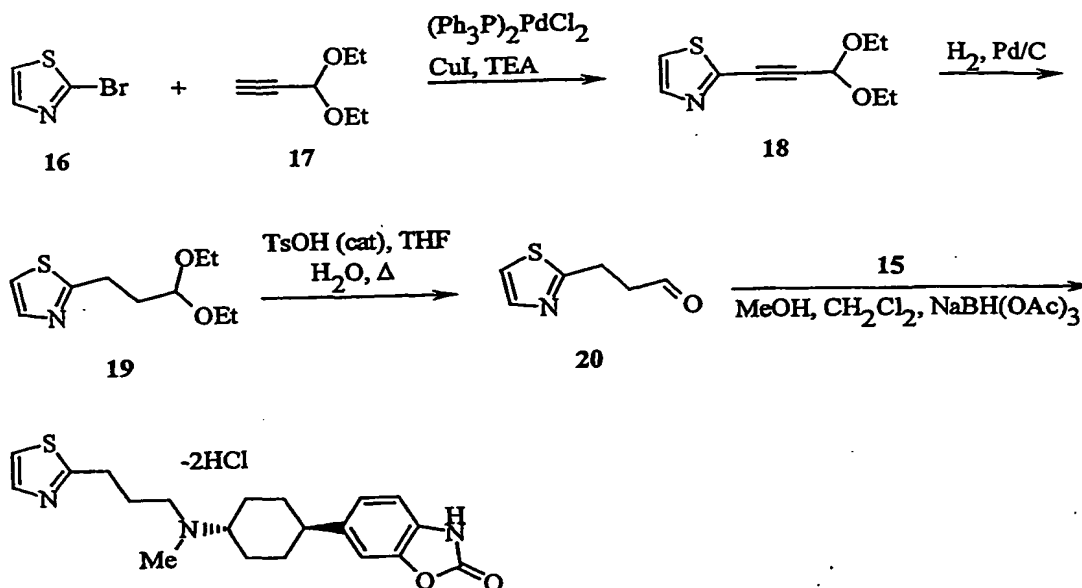


Condensation of 15 (2.22 g, 8.41 mmol) and 3-(4-dimethylaminophenyl)-propionaldehyde (910 mg, 5.14 mmol), following the procedure described in Example 45, Step 2, gave 6-(4-{{3-(*trans*-4-dimethylaminophenyl)propyl}-methylamino}cyclohexyl)-3*H*-benzoxazol-2-one (1.63 g, 78%), as an off-white solid: mp 182-184°C; IR (KBr): 2930, 1772, 1491, 1448  $cm^{-1}$ ;  $^1H$  NMR (500 MHz, DMSO- $d_6$ ):  $\delta$  11.4 (br s, 1H), 7.15 (s, 1H), 7.02-6.95 (m, 4H), 6.66 (d,  $J = 9$  Hz, 2H), 2.84 (s, 6H), 2.54-2.44 (m, 6H), 2.20 (s, 3H), 1.83-1.81 (m, 4H), 1.68-1.63 (m, 2H), 1.50-1.32 (m, 4H); ESI ( $m/z$ ): 408  $[M + H]^+$ ; HPLC: method A, 4.23 minutes (>99%); method B, 8.36 minutes (>99%); Anal. Calcd for  $C_{25}H_{33}N_3O_2 \cdot 0.5H_2O$ : C, 72.08; H, 8.23; N, 10.09. Found: C, 72.48; H, 8.09; N, 10.09.

## EXAMPLE 59

6-{*trans*-4-[Methyl(3-thiazol-2-ylpropyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one

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**Step 1:** To 2-bromothiazole 16 (5.0 g, 30 mmol) in DMF (40 mL) was added propiolaldehyde diethyl acetal 17 (4.4 g, 34 mmol), CuI (170 mg, 0.90 mmol), and triethylamine (8.4 mL, 60 mmol). The reaction mixture was deoxygenated with argon for 15 minutes, bis(triphenylphosphine)palladium (II) chloride (640 mg, 0.10 mmol) was added, and the mixture was deoxygenated again with argon for 15 minutes. After stirring at ambient temperature for 12 hours and then at 100°C for 2.5 hours, the reaction was cooled to ambient temperature, diluted with EtOAc (500 mL), washed with water (3 × 150 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 75:25 hexanes:EtOAc) gave alkyne 18 (3.4 g, 54%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.85 (d, *J* = 3 Hz, 1H), 7.39 (d, *J* = 3 Hz, 1H), 5.52 (s, 1H), 3.88-3.77 (m, 2H), 3.73-3.63 (m, 2H), 1.28 (t, *J* = 7 Hz, 6H).

**Step 2:** A mixture of alkyne 18 (1.1 g, 5.0 mmol) and 10% Pd/C (100 mg) in EtOH (20 mL) were shaken under a H<sub>2</sub> atmosphere at 50 psi for 5 hours. The solution was filtered through Celite and concentrated under reduced pressure. The residue was dissolved in EtOH (20 mL), 10% Pd/C (100 mg) was added, and the mixture was shaken again under a H<sub>2</sub> atmosphere at 50 psi for 5 hours. The solution was filtered through Celite and concentrated under reduced pressure to give acetal 19 (900 mg, 84%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.68 (d, *J* = 3 Hz,

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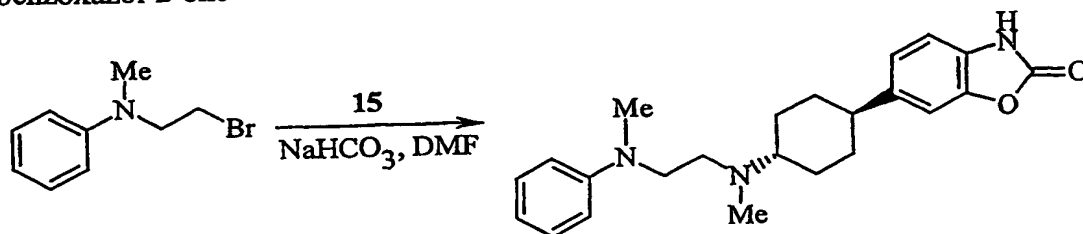
1H), 7.19 (d,  $J = 3$  Hz, 1H), 4.57 (t,  $J = 6$  Hz, 1H), 3.74-3.63 (m, 2H), 3.57-3.45 (m, 2H), 3.11 (t,  $J = 7$  Hz, 2H), 2.14 (dt,  $J = 14, 6$  Hz, 2H), 1.21 (t,  $J = 7$  Hz, 6H).

Step 3: To acetal 19 (450 mg, 2.1 mmol) in THF (10 mL) was added *p*-toluenesulfonic acid (20 mg, 0.10 mmol) and H<sub>2</sub>O (0.20 mL). The reaction mixture was heated at reflux for 45 minutes, cooled to ambient temperature, and concentrated under reduced pressure. Purification by flash chromatography (silica, 75:25 hexanes:EtOAc) gave aldehyde 20 (200 mg, 30%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 9.88 (s, 1H), 7.67 (d,  $J = 3$  Hz, 1H), 7.22 (d,  $J = 3$  Hz, 1H), 7.22 (d,  $J = 3$  Hz, 1H), 3.36 (t,  $J = 7$  Hz, 2H), 3.04 (t,  $J = 7$  Hz, 2H).

Step 4: Condensation of 15 (200 mg, 1.40 mmol) and aldehyde 20 (340 mg, 1.40 mmol), following the procedure described in Example 45, Step 2, followed by conversion to the HCl salt, gave 6-{*trans*-4-[methyl(3-thiazol-2-ylpropyl)-amino]cyclohexyl}-3*H*-benzoxazol-2-one (311 mg, 50%), as an off-white solid: mp 237-239°C; IR (KBr): 2948, 1767, 1499, 1449 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD): δ 8.04 (dd,  $J = 4, 1$  Hz, 1H), 7.87 (dd,  $J = 4, 1$  Hz, 1H), 7.14 (s, 1H), 7.08-6.99 (m, 2H), 3.53-3.20 (m, 5H), 2.89 (s, 3H), 2.69-2.61 (m, 1H), 2.40-2.26 (m, 2H), 2.24-2.14 (m, 2H), 2.10-2.01 (m, 2H), 1.86-1.61 (m, 4H); APCI ( $m/z$ ): 372 [M + H]<sup>+</sup>; HPLC: method A, 5.34 minutes (>99%); Anal. Calcd for C<sub>20</sub>H<sub>25</sub>N<sub>3</sub>O<sub>2</sub>S·2HCl: C, 54.05; H, 6.12; N, 9.46. Found: C, 53.82; H, 6.21; N, 9.22.

## EXAMPLE 60

6-(*trans*-4-{Methyl-[2-(Methylphenylamino)ethyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one

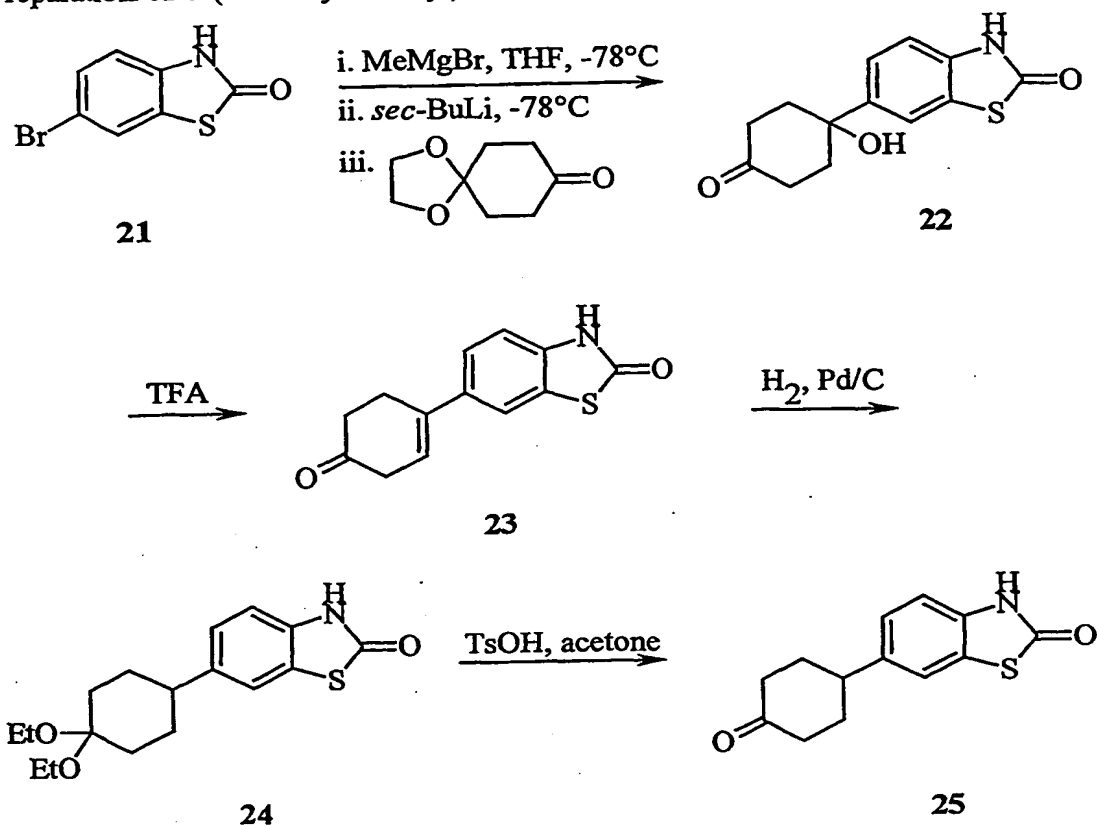


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**Step 1:** To a solution of amine 2 (780 mg, 3.2 mmol) in DMF (15 mL) was added NaHCO<sub>3</sub> (560 mg, 6.7 mmol) and (2-bromoethyl)methylphenylamine (690 mg, 3.2 mmol). The reaction mixture was gradually heated to 100°C, held at 100°C for 2.5 hours, and then stirred at 50°C for 12 hours. The suspension was cooled to room temperature, diluted with H<sub>2</sub>O (35 mL), and extracted with EtOAc (3 × 50 mL). The combined organics were washed with saturated NaCl (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 89:10:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH) followed by formation of the HCl salt and recrystallization (MeOH:Et<sub>2</sub>O) gave 6-(*trans*-4-{methyl-[2-(methylphenylamino)ethyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one (350 mg, 24%), as a white solid: mp 240-243°C; IR (KBr): 2950, 1765, 1499, 1451 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 8.72 (br s, 2H), 7.19-7.07 (m, 5H), 6.64 (d, *J* = 8 Hz, 2H), 6.57 (t, *J* = 11 Hz, 1H), 3.97 (t, *J* = 6 Hz, 2H), 3.67 (t, *J* = 6 Hz, 2H), 3.02-2.96 (m, 1H), 2.84 (s, 3H), 2.55 (m, 4H), 2.13 (br d, *J* = 10 Hz, 2H), 1.88 (br d, *J* = 10 Hz, 2H), 1.54-1.42 (m, 4H); HRMS-API (*m/z*): [M + H]<sup>+</sup> calcd for C<sub>23</sub>H<sub>29</sub>N<sub>3</sub>O<sub>2</sub>, 380.2338; found, 380.2339; HPLC: method A, 6.37 minutes (93.4%); method B, 11.60 minutes (93.0%); Anal. Calcd for C<sub>23</sub>H<sub>29</sub>N<sub>3</sub>O<sub>2</sub>·2HCl·0.25H<sub>2</sub>O: C, 60.46; H, 6.95; N, 9.20. Found: C, 60.65; H, 6.98; N, 9.12.

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## Scheme 4

Preparation of 6-(4-Oxocyclohexyl)-3*H*-benzothiazol-2-one 25

Step 1: Bromide 21 (2.88 g, 12.52 mmol) was dissolved in anhydrous THF (50 mL), and the solution was cooled to  $-78^\circ\text{C}$ . Solutions of MeMgBr (4.59 mL of a 3.0 M solution in Et<sub>2</sub>O, 13.77 mmol), *sec*-BuLi (10.59 mL of a 1.3 M solution in cyclohexane, 13.77 mmol), and 1,4-cyclohexanedione mono-ethylene ketal (1.95 g, 12.52 mmol) in anhydrous THF (10 mL) were added sequentially at 30-minute intervals. After the final addition, the reaction mixture was allowed to warm to room temperature. The reaction was quenched by the addition of 1N HCl (25 mL). The reaction mixture was diluted with EtOAc (300 mL), washed with saturated NaCl (250 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure. Purification by silica gel chromatography (eluent 1:1 Hexanes:EtOAc) gave alcohol 22 (1.81 g, 47%), as a white solid: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  8.48 (br s, 1H), 7.59 (s, 1H), 7.31 (d,  $J$  = 5 Hz, 1H), 7.04 (d,  $J$  = 5 Hz, 1H), 2.17-2.04 (m, 4H), 1.81 (d,  $J$  = 8 Hz, 2H), 1.77 (d,  $J$  = 8 Hz, 2H).

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Step 2: Alcohol 22 (1.81 g, 5.90 mmol) was stirred in TFA (8 mL) at room temperature for 20 minutes. The red solution was poured into CHCl<sub>3</sub> (200 mL), and the organic layer was washed with H<sub>2</sub>O (2 × 100 mL), saturated NaHCO<sub>3</sub> and saturated NaCl, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure to give ketone 23 (1.22 g, 85%), as a white solid: <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 7.42 (s, 1H), 7.34 (d, *J* = 6 Hz, 1H), 7.08 (d, *J* = 6 Hz, 1H), 6.11 (t, *J* = 5 Hz, 1H), 3.04 (d, *J* = 2 Hz, 2H), 2.87 (t, *J* = 7 Hz, 2H), 2.57 (m, 2H).

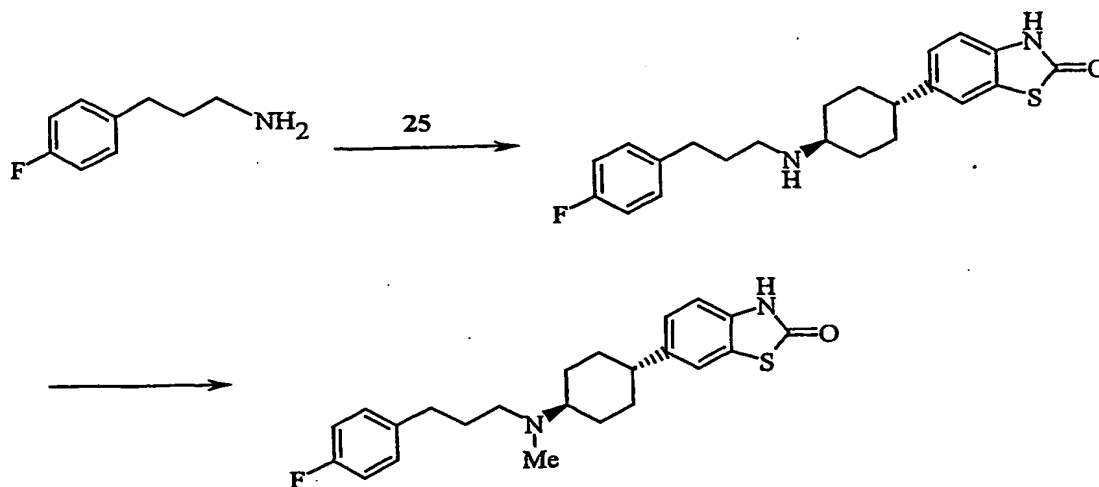
Step 3: A solution of ketone 23 (1.22 g, 4.98 mmol) and 10% Pd/C (0.25 g) in a 3:2 mixture of EtOAc:EtOH (150 mL) was shaken under a H<sub>2</sub> atmosphere at 50 psi for 4 hours. The solution was filtered through Celite and concentrated under reduced pressure. Purification by flash chromatography (eluent 1.5:1 Hexanes:EtOAc) gave ketal 24 (1.44 g, 98%) as a white solid: <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD): δ 7.31 (s, 1H), 7.13 (d, *J* = 6 Hz, 1H), 7.04 (d, *J* = 6 Hz, 1H), 3.53 (q, *J* = 7 Hz, 2H), 3.48 (q, *J* = 7 Hz, 2H), 2.57 (m, 1H), 2.10 (d, *J* = 10 Hz, 2H), 1.76-1.51 (m, 4H), 1.47 (m, 2H), 1.21 (t, *J* = 7 Hz, 3H), 1.18 (t, *J* = 7 Hz, 3H).

Step 4: Ketal 24 (0.6 g, 1.9 mmol) and TsOH (0.36 g, 1.89 mmol) were stirred in acetone (20 mL) overnight. The reaction mixture was diluted with EtOAc (100 mL) and washed with H<sub>2</sub>O (50 mL) and saturated NaHCO<sub>3</sub> (50 mL). The organic layer was concentrated under reduced pressure to give 6-(4-oxocyclohexyl)-3*H*-benzothiazol-2-one 25 (0.48 g, 98%) as a white solid: <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD): δ 7.41 (s, 1H), 7.21 (d, *J* = 6 Hz, 1H), 7.06 (d, *J* = 6 Hz, 1H), 3.13 (m, 1H), 2.53 (m, 2H), 2.31 (m, 2H), 2.14 (m, 2H), 1.96 (m, 2H).

## EXAMPLE 61

- (a) 6-{*trans*-4-[3-(4-Fluorophenyl)propylamino]cyclohexyl}-3*H*-benzthiazol-2-one
- (b) 6-(*trans*-4-[[3-(4-Fluorophenyl)propyl]methylamino]cyclohexyl)-3*H*-benzthiazol-2-one

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**Step 1:** To a solution of ketone **25** (2.3 g, 9.3 mmol) in 2-propanol (30 mL) was added 4Å molecular sieves and 3-(4-fluorophenyl)-1-propylamine (1.76 g, 9.3 mmol). The reaction mixture was stirred for 4 hours. Sodium borohydride (0.49 g, 13.03 mmol) was added, and the reaction mixture was stirred overnight, quenched with MeOH, and concentrated under reduced pressure. Purification by flash chromatography (silica, 9.5:5:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH) gave 6-{*trans*-4-[3-(4-fluorophenyl)propylamino]cyclohexyl}-3*H*-benzthiazol-2-one (0.24 g, 7%): <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 7.39 (s, 1H), 7.25-7.06 (m, 6H), 3.01 (m, 1H), 2.86 (t, *J* = 8 Hz, 2H), 2.61 (t, *J* = 8 Hz, 2H), 2.37 (m, 1H), 2.01 (m, 2H), 1.92-1.81 (m, 4H), 1.49-1.36 (m, 4H).

**Step 2:** To a stirred solution of 6-{*trans*-4-[3-(4-fluorophenyl)propylamino]cyclohexyl}-3*H*-benzthiazol-2-one (0.24 g, 0.67 mmol) in MeOH (10 mL) containing H<sub>2</sub>O (0.5 mL) was added *p*-formaldehyde (0.1 g, 3.3 mmol). The reaction mixture was stirred for 3 hours. Sodium triacetoxyborohydride (0.2 g, 0.9 mmol) was added, and the mixture was stirred overnight. Solid NaOH was added until the solution became clear. The reaction mixture was concentrated under reduced pressure to give a yellow oil. Purification by flash chromatography (eluent 9.5:1:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH) gave 6-(*trans*-4-{[3-(4-fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzthiazol-2-one (55 mg, 15%), as a pale yellow solid: mp 256-261°C; IR (KBr): 2942, 1683, 1509 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 7.41 (s, 1H), 7.31-7.03 (m, 6H), 3.29 (m, 2H), 3.01 (m, 2H), 2.70 (s, 3H), 2.64 (m, 2H), 2.11 (m, 1H), 2.08 (m, 1H), 1.99 (m, 2H),

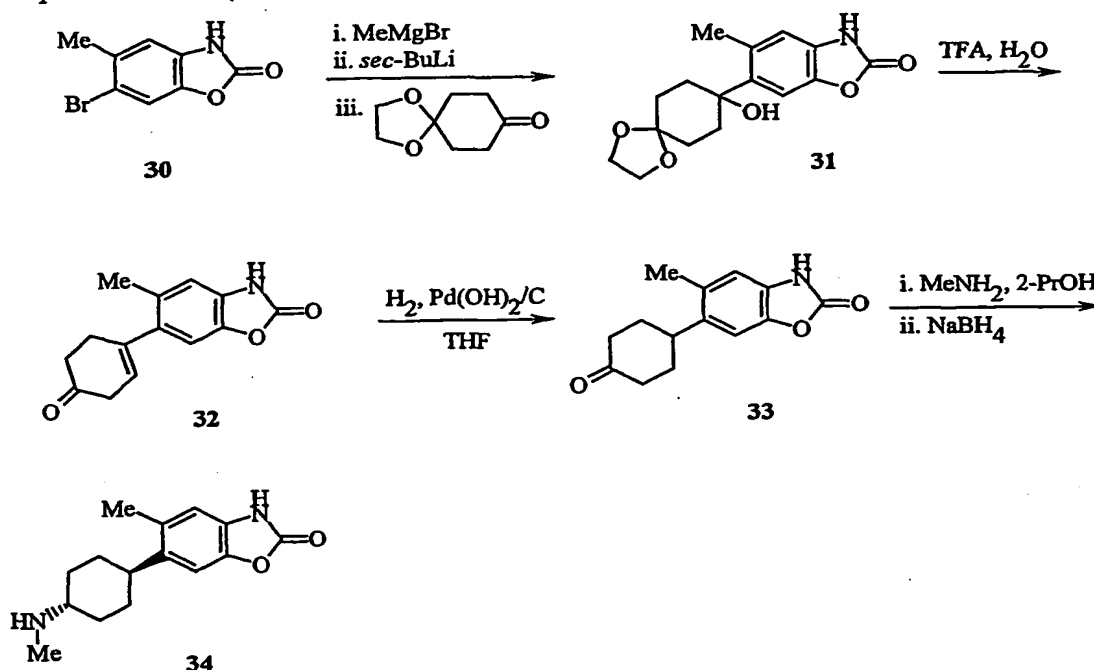


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1.87 (m, 2H), 1.98-1.61 (m, 4H); API-MS ( $m/z$ ): 399  $[M + H]^+$ ; calcd for  $C_{23}H_{27}FN_2OS$ , 399.1906; found, 399.1909; HPLC: method A, 5.85 minutes (>99%); method B, 11.48 minutes (>99%); Anal. Calcd for  $C_{23}H_{27}FN_2OS \cdot HCl \cdot 0.75NaCl$ : C, 57.69; H, 5.89; N, 5.85. Found: C, 57.72; H, 5.96; N, 5.51.

## Scheme 5

Preparation of 5-(4-Oxocyclohexyl)-1,3-dihydrobenzimidazol-2-one 29



**Step 1:** *N*-Bromosuccinimide (112.0 g, 0.63 mol) was added to a stirred solution of 2-hydroxybenzimidazole 26 (84.4 g, 0.63 mol) in glacial acetic acid (930 mL), and the mixture was stirred at room temperature for 12 hours. The reaction mixture was poured into H<sub>2</sub>O (3 L), and the yellow solid that formed was collected. Trituration with hot EtOH (1.5 L) gave bromide 27 (113.2 g, 85%), as yellow solid: <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 10.75 (s, 2H), 7.11-7.05 (m, 2H), 6.87 (d, *J* = 9 Hz, 2H).

**Step 2:** Bromide 27 (25.0 g, 0.12 mol) was dissolved in anhydrous THF (1.5 L) and the solution was cooled in a -78°C dry ice/2-PrOH bath. A solution of

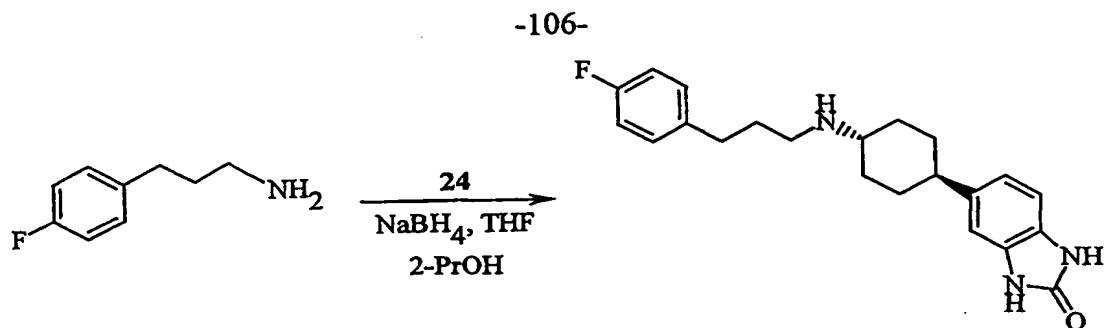
-105-

MeMgBr (43.0 mL of a 3.0 M solution in Et<sub>2</sub>O, 0.13 mol) was added dropwise over 10 minutes, (internal temperature maintained -60°C). After stirring at -78°C for 1 hour, *t*-BuLi (289.4 mL of a 1.7 M solution in pentane, 0.49 mol) was added dropwise over 0.5 hours (again, temperature was maintained below -60°C). After 0.75 hours, 1,4-cyclohexanedione mono-ethylene ketal (37.5 g, 0.24 mol) in anhydrous THF (120 mL) was added over 10 minutes. After 0.5 hours, the reaction mixture was warmed to 0°C. The reaction was quenched by the addition of saturated aqueous NH<sub>4</sub>Cl (210 mL), and the solution was warmed to room temperature. Most of the THF was removed under reduced pressure, 1N HCl (500 mL) was added, and mixture was extracted with EtOAc (5 × 200 mL). The combined organics were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure. The residue was slurried in EtOAc, and the resulting solid was collected by vacuum filtration and dried (21.4 g). This solid was stirred in TFA (50 mL) at room temperature for 20 minutes. The red solution was poured into CHCl<sub>3</sub> (400 mL) and H<sub>2</sub>O (400 mL). A gelatinous solid formed which was collected by vacuum filtration, rinsed with H<sub>2</sub>O (150 mL), and dried to give crude 28 (25.5 g, 92%). <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 10.78 (s, 1H), 10.60 (s, 1H), 7.01-6.85 (m, 3H), 6.05-6.00 (m, 1H), 3.05-3.00 (m, 2H), 2.88-2.79 (m, 2H), 2.59-2.52 (m, 2H).

**Step 3:** A mixture of crude 28 (0.85 g, 3.7 mmol) and 10% Pd/C (0.15 g) in EtOH (30 mL) was shaken under a H<sub>2</sub> atmosphere at 50 psi for 3 hours. The solution was filtered through Celite and concentrated under reduced pressure to give crude 5-(4-oxocyclohexyl)-1,3-dihydrobenzoimidazol-2-one 29 (850 mg, 99%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 6.95-6.80 (m, 3H), 3.07-2.95 (m, 1H), 2.67-2.48 (m, 2H), 2.32-2.22 (m, 2H), 2.09-1.97 (m, 2H), 1.90-1.65 (m, 2H).

## EXAMPLE 62

5-{*trans*-4-[3-(4-Fluorophenyl)propylamino]cyclohexyl}-1,3-dihydrobenzoimidazol-2-one

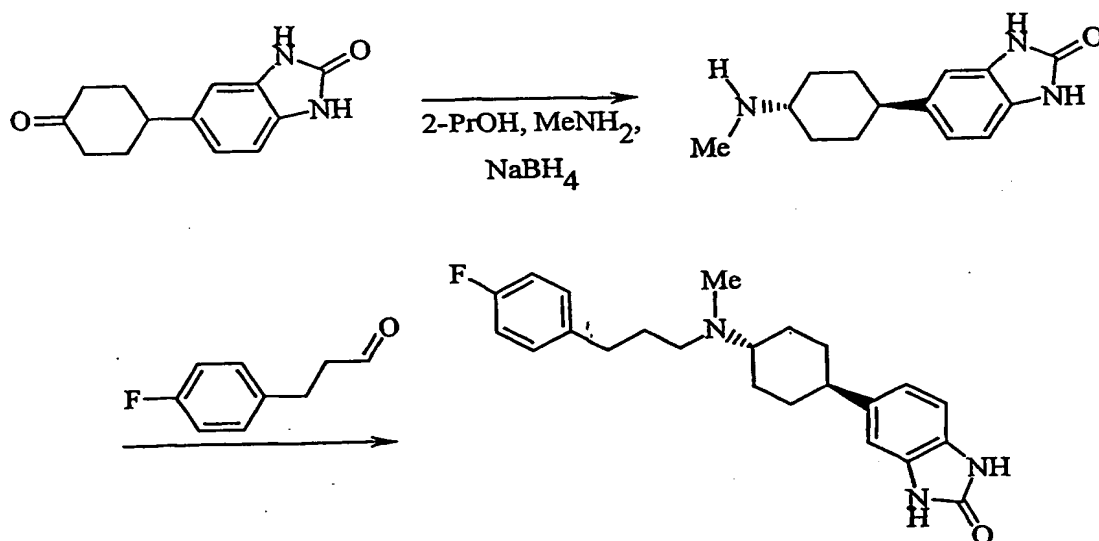


To a solution of (4-fluorophenyl)-1-propylamine (1.9 g, 10.0 mmol) in 2-propanol (90 mL) and THF (25 mL) was added Et<sub>3</sub>N (1.5 mL, 11.0 mmol), ketone 24 (2.3 g, 10.0 mmol), and 3Å molecular sieves. The reaction mixture was stirred at room temperature for 3 hours. Sodium borohydride (950 mg, 25.1 mmol) was added, and the reaction mixture was stirred for 12 hours. Additional sodium borohydride (500 mg, 13.2 mmol) was added, and the reaction mixture was stirred for 12 hours. Methanol was added to quench the excess NaBH<sub>4</sub>, and the resultant solution was filtered through a pad of Celite and concentrated under reduced pressure. Purification by flash chromatography (silica, 90:10 CH<sub>2</sub>Cl<sub>2</sub>:MeOH followed by 95:4.5:0.5 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH), followed by formation of the HCl salt and recrystallization (MeOH:Et<sub>2</sub>O), gave 5-{*trans*-4-[3-(4-fluorophenyl)propylamino]cyclohexyl}-1,3-dihydrobenzoimidazol-2-one (162 mg, 4%), as a white solid: mp 336-339°C; IR (KBr): 2943, 1727, 1686, 1510 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 10.45 (s, 1H), 10.39 (s, 1H), 8.55 (s, 2H), 7.29-7.27 (m, 2H), 7.15-7.12 (m, 2H), 6.83-6.76 (m, 3H), 3.13-3.06 (m, 1H), 2.97-2.89 (m, 2H), 2.68 (t, *J* = 8 Hz, 2H), 2.48-2.44 (m, 1H), 2.15-2.08 (m, 2H), 1.97-1.82 (m, 4H), 1.54-1.43 (m, 4H); API (*m/z*): 368 [M + H]<sup>+</sup>; HPLC: method A, 5.07 minutes (98.8%); method B, 11.00 minutes (98.9%); Anal. Calcd for C<sub>22</sub>H<sub>26</sub>FN<sub>3</sub>O·HCl·0.25H<sub>2</sub>O: C, 64.70; H, 6.79; N, 10.29. Found: C, 64.79; H, 6.74; N, 10.12.

### EXAMPLE 63

5-(*trans*-4-{[3-(4-Fluorophenyl)propyl]methylamino}cyclohexyl)-1,3-dihydrobenzoimidazol-2-one

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**Step 1:** To a suspension of ketone 29 (2.15 mg, 9.4 mmol) in 2-PrOH (115 mL, HPLC grade) was added methylamine (7.1 mL of a 2.0 M solution in THF, 14.2 mmol). After 1 hour, the reaction mixture was cooled in an ice/water bath and sodium borohydride (530 mg, 14.0 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 12 hours. Methanol (ca 2 mL) was added to quench any excess sodium borohydride, and the solvents were removed under reduced pressure. Purification by flash chromatography (silica, 89:10:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH) followed by formation of the HCl salt and recrystallization (MeOH:Et<sub>2</sub>O) gave 5-(4-methylaminocyclohexyl)-1,3-dihydrobenzimidazol-2-one (402 mg, 13%): <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 10.58 (s, 1H), 10.51 (s, 1H), 8.81 (s, 2H), 6.99-6.71 (m, 3H), 3.05-2.90 (m, 1H), 2.20-2.09 (m, 2H), 2.48-2.50 (m, 4H), 1.95-1.85 (m, 2H), 1.57-1.39 (m, 4H).

**Step 2:** To a suspension of 5-(4-methylaminocyclohexyl)-1,3-dihydrobenzimidazol-2-one (400 mg, 1.4 mmol) in 1:1 CH<sub>2</sub>Cl<sub>2</sub>:MeOH (32 mL) was added 3-(4-fluorophenyl)propionaldehyde (220 mg, 1.4 mmol) and, after 5 minutes, NaBH(OAc)<sub>3</sub> (420 mg, 2.0 mmol). After 12 hours NaBH(OAc)<sub>3</sub> (300 mg, 1.4 mmol) was added and stirring continued for 8.25 hours. The reaction mixture was brought to pH 8 with solid NaOH and concentrated under reduced pressure. Purification by flash chromatography (silica, 95:4.5:0.5 CH<sub>2</sub>Cl<sub>2</sub>:MeOH:NH<sub>4</sub>OH) and formation of the HCl salt gave 5-(trans-4-{[3-(4-fluorophenyl)propyl]methylamino}cyclohexyl)-1,3-dihydrobenzimidazol-2-one.

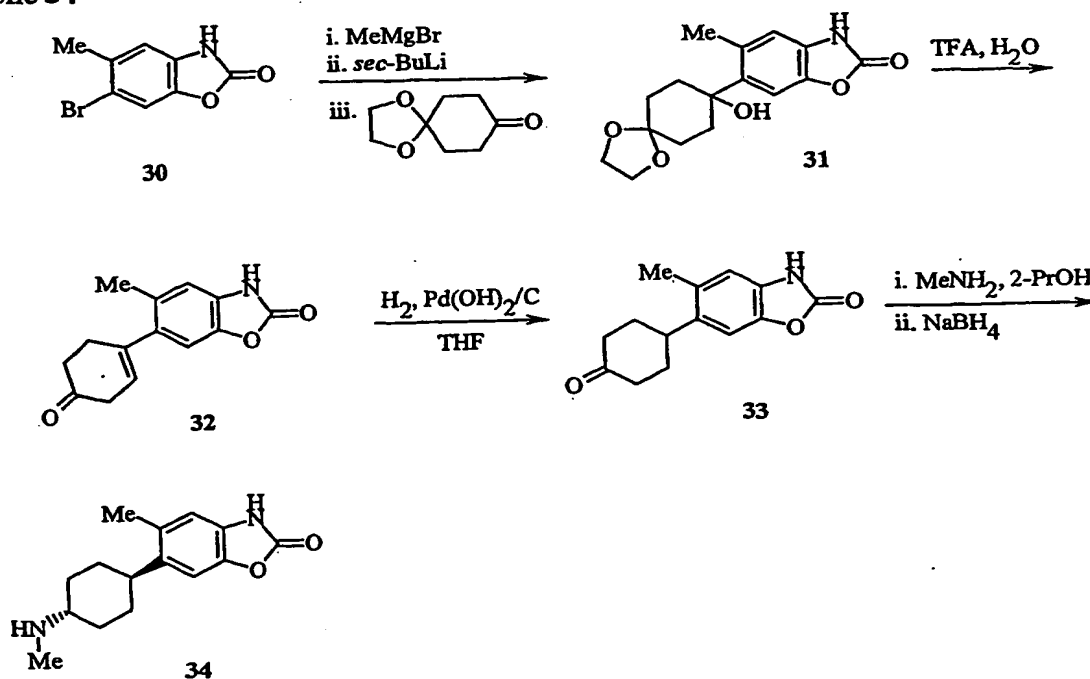
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dihydrobenzoimidazol-2-one (330 mg, 56%), as an off-white foam: IR (KBr): 2949, 1696  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  10.52 (s, 1H), 10.48 (s, 1H), 10.42 (s, 1H), 7.31-7.28 (m, 2H), 7.17-7.11 (m, 2H), 6.87-6.76 (m, 3H), 3.35-3.25 (m, 1H), 3.18-3.09 (m, 1H), 3.02-2.59 (m, 1H), 2.71-2.61 (m, 5H), 2.48-2.45 (m, 1H), 2.19-1.99 (m, 4H), 1.92-1.85 (m, 2H), 1.68-1.49 (m, 4H); ESI ( $m/z$ ): 382 [ $\text{M} + \text{H}$ ] $^+$ ; HRMS-API ( $m/z$ ): [ $\text{M} + \text{H}$ ] $^+$  calcd for  $\text{C}_{23}\text{H}_{28}\text{FN}_3\text{O}$ , 382.2294; found, 382.2292; method A, 5.64 minutes (>99%); method B, 10.82 minutes (>99%); Anal. Calcd for  $\text{C}_{23}\text{H}_{28}\text{FN}_3\text{O} \cdot \text{HCl} \cdot 0.75\text{H}_2\text{O}$ : C, 64.03; H, 7.13; N, 9.74. Found: C, 63.89; H, 7.22; N, 9.50.

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## Scheme 6

Preparation of 5-Methyl-6-(*trans*-4-methylaminocyclohexyl)-3*H*-benzoxazol-2-one 34



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Step 1: Bromide 30 (5.0 g, 21.9 mmol) was dissolved in anhydrous THF (85 mL), and the solution was cooled to  $-78^\circ\text{C}$ . Solutions of MeMgBr (8.03 mL of a 3.0 M solution in  $\text{Et}_2\text{O}$ , 24.1 mmol), *sec*-BuLi (18.5 mL of a 1.3 M solution in cyclohexane, 24.1 mmol), and 1,4-cyclohexanedione monoethylene ketal (3.76 g, 24.1 mmol) in anhydrous THF (20 mL) were added sequentially at 30-minute

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intervals. After the final addition, the reaction mixture was allowed to warm to room temperature. The reaction mixture was diluted with EtOAc (500 mL), washed with saturated NaCl (200 mL), and the water layer was extracted with EtOAc (200 mL) and CH<sub>2</sub>Cl<sub>2</sub> (200 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure to provide a crude solid which was purified by flash chromatography (silica, 10% MeOH:CH<sub>2</sub>Cl<sub>2</sub>) to yield **31** (2.96 g, 44%), as a white solid: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 8.85 (br s, 1H), 7.38 (s, 1H), 6.83 (s, 1H), 4.03-3.90 (m, 4H), 2.61 (s, 3H), 2.23 (dt, *J* = 13, 4 Hz, 2H), 2.12 (dt, *J* = 13, 4 Hz, 2H), 1.96-1.90 (m, 2H), 1.73-1.61 (m, 2H).

**Step 2:** Compound **31** was stirred in TFA (12 mL) and H<sub>2</sub>O (3 mL) and slowly warmed from 0°C to room temperature over 3.5 hours. The red solution was poured into CHCl<sub>3</sub> (300 mL), and the organic layer was washed with H<sub>2</sub>O (2 × 100 mL), saturated NaHCO<sub>3</sub>, and saturated NaCl, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure to give **32** (2.13 g, 91%), as a white solid: <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD): δ 6.98 (s, 1H), 6.91 (s, 1H), 5.68 (t, *J* = 3 Hz, 1H), 3.06-3.02 (m, 2H), 2.73-2.65 (m, 2H), 2.64-2.61 (m, 2H), 2.34 (s, 3H).

**Step 3:** A mixture of **32** (1.64 g, 6.74 mmol) in THF (100 mL) and 20% Pd(OH)<sub>2</sub>/C (490 mg) was shaken under a H<sub>2</sub> atmosphere at 50 psi for 12 hours. The solution was filtered through Celite and concentrated under reduced pressure to give **33** (1.70 g, 100%) as a pale yellow solid: <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD): δ 7.11 (s, 1H), 6.90 (s, 1H), 3.36 (tt, *J* = 13, 3 Hz, 1H), 2.65 (dt, *J* = 13, 6 Hz, 2H), 2.45-2.39 (m, 5H), 2.15-2.08 (m, 2H), 1.90 (ddd, *J* = 17, 13, 4 Hz, 2H).

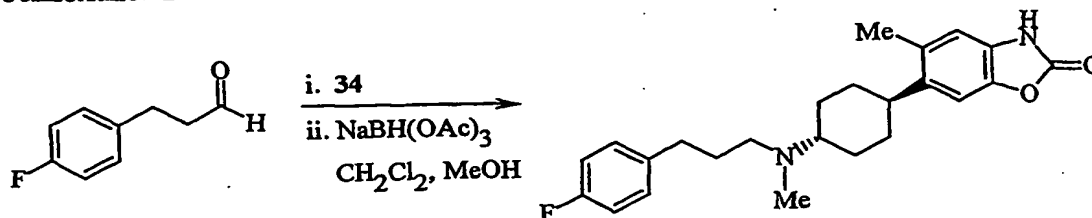
**Step 4:** Condensation of **33** (1.65 g, 6.74 mmol) with methylamine (5.06 mL, 10.1 mmol) and NaBH<sub>4</sub> (382 mg, 10.1 mmol) in 2-propanol (28 mL), following the procedure described in Example 63, Step 1, gave 5-methyl-6-(*trans*-4-methylaminocyclohexyl)-3*H*-benzoxazol-2-one (**34**) (207 mg, 12%), as a white solid: <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 7.08 (s, 1H), 6.82 (s, 1H), 2.63 (tt, *J* = 12, 3 Hz, 1H), 2.35 (tt, *J* = 11, 4 Hz, 1H), 2.32 (s, 3H), 2.28 (s, 3H), 1.98 (br d,

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$J = 12$  Hz, 2H), 1.68 (br d,  $J = 12$  Hz, 2H), 1.44 (ddd,  $J = 16, 13, 3$  Hz, 2H), 1.13 (ddd,  $J = 16, 13, 3$  Hz, 2H).

## EXAMPLE 64

6-(4-{[3-(4-Fluorophenyl)propyl]methyl-amino}cyclohexyl)-5-methyl-3H-benzoxazol-2-one

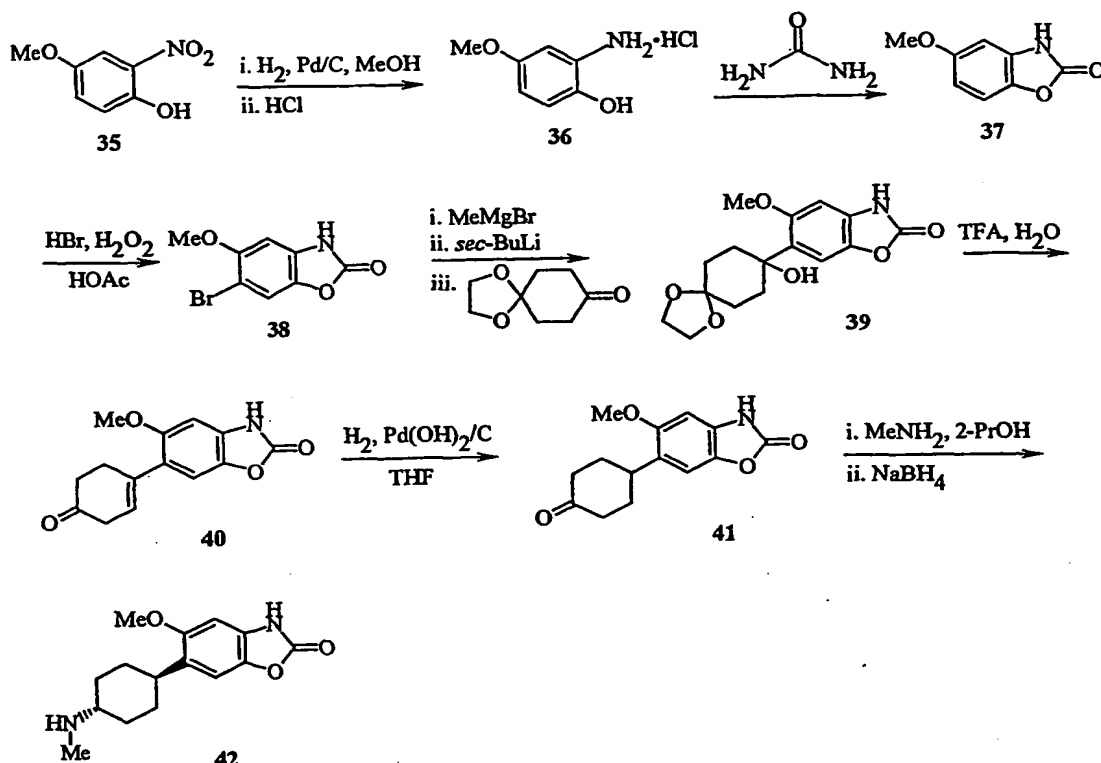


Condensation of 5-methyl-6-(*trans*-4-methylaminocyclohexyl)-3H-benzoxazol-2-one 34 (0.20 g, 0.77 mmol) with 3-(4-fluorophenyl)propionaldehyde 25 (0.13 g, 0.85 mmol) and NaBH(OAc)<sub>3</sub> (229 mg, 1.08 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) and MeOH (4 mL), following the procedure described in Example 63, Step 2, gave 6-(4-{[3-(4-fluorophenyl)propyl]methyl-amino}cyclohexyl)-5-methyl-3H-benzoxazol-2-one (190 mg, 62%), as a white solid: mp 264-267°C; IR (KBr): 2953, 1765, 1510, 1491 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 11.40 (s, 1H), 10.01 (s, 1H), 7.31 (dd,  $J = 8, 6$  Hz, 2H), 7.14 (t,  $J = 9$  Hz, 2H), 7.11 (s, 1H), 6.88 (s, 1H), 3.35-3.28 (m, 1H), 3.19-3.12 (m, 1H), 3.05-2.98 (m, 1H), 2.72 (d,  $J = 5$  Hz, 3H), 2.69-2.62 (m, 2H), 2.53-2.46 (m, 1H), 2.29 (s, 3H), 2.14-1.97 (m, 4H), 1.85-1.78 (m, 2H), 1.72-1.50 (m, 4H); ESI ( $m/z$ ): 397 [M + H]<sup>+</sup>; HPLC: method A, 6.37 minutes (>99%); Anal. Calcd for C<sub>24</sub>H<sub>29</sub>FN<sub>2</sub>O<sub>2</sub>·HCl: C, 66.58; H, 6.98; N, 6.47. Found: C, 66.47; H, 7.02; N, 6.32.

## Scheme 7

Preparation of 5-Methoxy-6-(4-methylaminocyclohexyl)-3H-benzoxazol-2-one 42

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**Step 1:** To a solution of 4-methoxy-2-nitrophenol **35** (10.0 g, 59.1 mmol) in MeOH (500 mL) was added 10% Pd/C (1.0 g), and the reaction was stirred under a  $\text{H}_2$  atmosphere at balloon pressure for 4 hours. The reaction was acidified with HCl (60 mL of a 1N solution in  $\text{Et}_2\text{O}$ , 60 mmol), and then filtered through Celite. Concentration under reduced pressure gave **36** (10.4 g, 100%), which was used without further purification:  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  6.96-6.87 (m, 3H), 3.75 (s, 3H).

**Step 2:** A mixture of salt **36** (10.3 g, 58.7 mmol) and urea (5.64 g, 93.9 mmol) was heated at  $180^\circ\text{C}$  for 2 hours. After the reaction was cooled to room temperature, 1N HCl was added, and the water layer was extracted with EtOAc. The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ) and filtered. Concentration under reduced pressure gave **37** (7.46 g, 77%), which was used without further purification:  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.14-7.06 (m, 1H), 6.68-6.62 (m, 2H), 3.78 (s, 3H).

**Step 3:** To a solution of **37** (8.27 g, 50.1 mmol) in HOAc (30 mL) were added hydrogen bromide (22.9 mL, 115 mmol) and hydrogen peroxide (6.55 mL,



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64.1 mmol) at 10°C. The reaction was allowed to warm to room temperature and then stirred 1 hour. Water (50 mL) was added to the reaction mixture. The dark gray solid which formed was collected by filtration, and then washed with H<sub>2</sub>O (50 mL). The crude solid was dissolved in hot EtOH, and hexane was added until a precipitate formed. The precipitate was collected by filtration to **38** (9.44 g, 77%): <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 7.42 (s, 1H), 6.83 (s, 1H), 3.84 (s, 3H).

**Step 4:** Condensation of **38** (3.36 g, 13.8 mmol) with 1,4-cyclohexanedione monoethylene ketal (2.37 g, 15.2 mmol), following the procedure described in Step 2, Scheme 2, gave **39** (3.12 g, 70%), as a brown foam: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 9.80 (br s, 1H), 7.22 (s, 1H), 6.74 (s, 1H), 4.02-3.93 (m, 4H), 3.92 (s, 3H), 3.49 (s, 1H), 2.22-2.13 (m, 2H), 2.09-2.05 (m, 4H), 1.70-1.65 (m, 2H).

**Step 5:** The reaction of **39** (3.12 g, 9.71 mmol) in TFA (12 mL) and H<sub>2</sub>O (3 mL), following the procedure described in Step 3, Scheme 2, gave **40** (2.50 g, 99%) as a pale yellow solid: <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD): δ 7.04 (s, 1H), 6.75 (s, 1H), 5.78 (t, *J* = 3 Hz, 1H), 3.83 (s, 3H), 3.06-3.02 (m, 2H), 2.80-2.75 (m, 2H), 2.58 (t, *J* = 7 Hz, 2H).

**Step 6:** A mixture of **40** (2.50 g, 9.64 mmol) in THF (150 mL) and 20% Pd(OH)<sub>2</sub>/C (700 mg) was shaken under a H<sub>2</sub> atmosphere at 50 psi for 12 hours. The solution was filtered through Celite and concentrated under reduced pressure to give **41** (1.56 g, 62%), as a mustard-colored solid: <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD): δ 7.10 (s, 1H), 6.77 (s, 1H), 3.86 (s, 3H), 3.52 (tt, *J* = 9, 3 Hz, 1H), 2.60 (ddd, *J* = 14, 14, 6 Hz, 2H), 2.40 (dt, *J* = 15, 2 Hz, 2H), 2.15-2.08 (m, 2H), 1.91-1.85 (m, 2H).

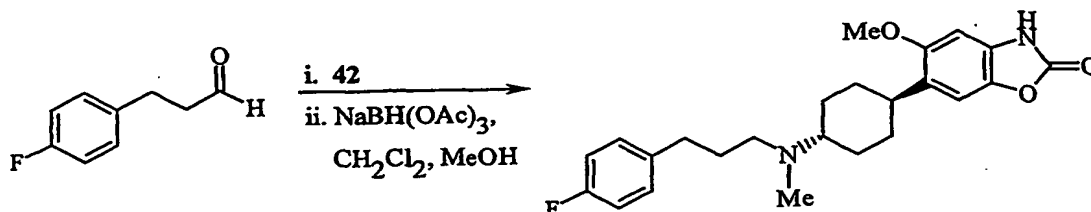
**Step 7:** Condensation of **41** (2.49 g, 9.53 mmol) with methylamine (7.2 mL, 14.3 mmol) and NaBH<sub>4</sub> (541 mg, 14.3 mmol) in 2-propanol (40 mL), following the procedure described in Example 63, Step 1, gave 5-methoxy-6-(4-methylaminocyclohexyl)-3*H*-benzoxazol-2-one **42** (200 mg, 12%), as a white solid: <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 7.05 (s, 1H), 6.67 (s, 1H), 3.78 (s, 3H),

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2.83 (tt,  $J = 9$ , 3 Hz, 1H), 2.36-2.31 (m, 1H), 2.30 (s, 3H), 1.98 (br d,  $J = 12$  Hz, 2H), 1.70 (br d,  $J = 12$  Hz, 2H), 1.47-1.35 (m, 2H), 1.15-1.05 (m, 2H).

## EXAMPLE 65

6-(*trans*-4-{[3-(4-Fluorophenyl)propyl]methylamino}cyclohexyl)-5-methoxy-3*H*-benzoxazol-2-one

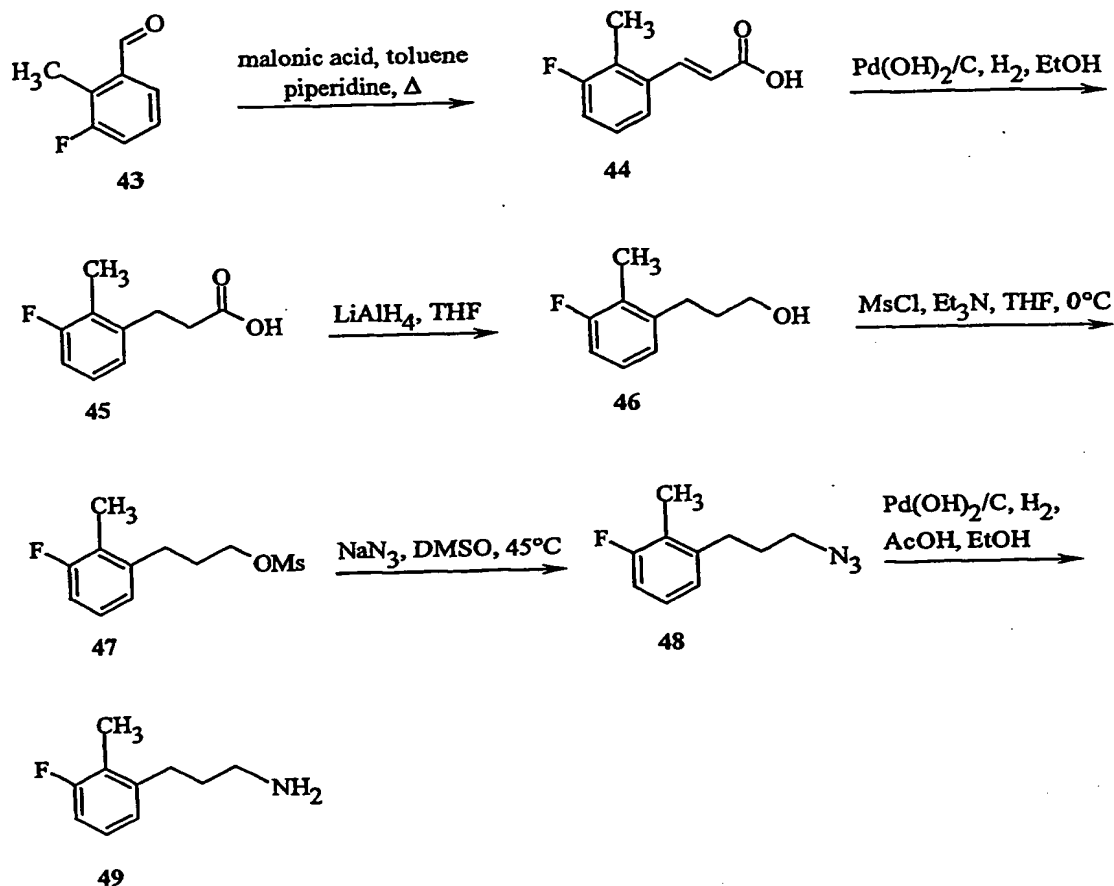


Condensation of 5-methoxy-6-(4-methylaminocyclohexyl)-3*H*-benzoxazol-2-one **42** (0.20 g, 0.72 mmol) with 3-(4-fluorophenyl)propionaldehyde **25** (0.12 g, 0.79 mmol) and NaBH(OAc)<sub>3</sub> (214 mg, 1.01 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (4 mL) and MeOH (4 mL), following the procedure described in Example 63, Step 2, gave 6-(*trans*-4-{[3-(4-fluorophenyl)propyl]methylamino}-cyclohexyl)-5-methoxy-3*H*-benzoxazol-2-one (236 mg, 79%), as an off-white solid: mp 239-242°C; IR (KBr): 3435, 2945, 1767, 1510, 1495 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 11.50 (s, 1H), 10.35 (br s, 1H), 7.29 (dd,  $J = 9$ , 6 Hz, 2H), 7.13 (t,  $J = 9$  Hz, 2H), 7.08 (s, 1H), 6.72 (s, 1H), 3.35-3.30 (m, 1H), 3.28 (s, 3H), 3.19-3.12 (m, 1H), 3.02-2.95 (m, 1H), 2.90 (tt,  $J = 12$ , 9 Hz, 3H), 2.68 (d,  $J = 5$  Hz, 3H), 2.68-2.62 (m, 2H), 2.15-1.95 (m, 4H), 1.85-1.77 (m, 2H), 1.69-1.45 (m, 4H); ESI ( $m/z$ ): 413 [ $M + H$ ]<sup>+</sup>; HPLC: method A, 6.31 minutes (>99%), method B, 11.6 minutes (>99%); Anal. Calcd for C<sub>24</sub>H<sub>29</sub>FN<sub>2</sub>O<sub>3</sub>·HCl·H<sub>2</sub>O: C, 61.73; H, 6.91; N, 6.00. Found: C, 61.85; H, 6.96; N, 5.87.

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## Scheme 8

## General Procedure for the Preparation of Aryl Amines and Aldehydes



Step 1: A mixture of 3-fluoro-2-methylbenzaldehyde (10 g, 72 mmol),  
 malonic acid (8.3 g, 80 mmol), piperidine (0.35 mL, 3.6 mmol), and toluene  
 (150 mL) was heated to reflux (flask equipped with a Dean-stark trap) for  
 22 hours. After cooling to ambient temperature, the reaction mixture was  
 extracted with saturated  $\text{NaHCO}_3$  ( $2 \times 30$  mL), brought to pH 3 with 1N HCl, and  
 extracted with EtOAc ( $3 \times 50$  mL). The combined organic extracts were dried  
 ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated under reduced pressure to give cinnamic  
 acid 44 (5.2 g, 40%) which was used without further purification:  $^1\text{H}$  NMR  
 (500 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  12.48 (s, 1H), 7.79 (d,  $J = 16$  Hz, 1H), 7.53 (d,  
 $J = 8$  Hz, 1H), 7.26 (dd,  $J = 8, 8$  Hz, 1H), 7.19 (dd,  $J = 8, 8$  Hz, 1H), 6.45 (d,  
 $J = 16$  Hz, 1H), 2.26 (s, 3H).

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**Step 2:** A mixture of cinnamic acid **44** (5.2 g, 29 mmol) and 20% Pd(OH)<sub>2</sub>/C (100 mg) in EtOH (150 mL) was shaken under a H<sub>2</sub> atmosphere (balloon) for 22 hours. The solution was filtered through Celite and concentrated under reduced pressure to give acid **45** (5.2 g, 100%), which was used without further purification: <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 12.15 (s, 1H), 7.14 (dd, *J* = 8, 8 Hz, 1H), 7.00 (d, *J* = 8 Hz, 1H), 6.97 (dd, *J* = 8, 8 Hz, 1H), 2.84 (dd, *J* = 8, 7 Hz, 2H), 2.48 (dd, *J* = 8, 7 Hz, 2H), 2.17 (d, *J* = 2 Hz, 3H).

**Step 3:** To an ice-cold, stirred solution of acid **45** (5.1 g, 28 mmol) in THF (50 mL) was added LiAlH<sub>4</sub> (1.1 g, 28 mmol) portionwise over 10 minutes. After stirring for 1 hour, the reaction mixture was carefully quenched with methanol, diluted with EtOAc, filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was taken up in EtOAc, washed with 1N HCl, H<sub>2</sub>O, saturated NaCl, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 95:5 methylene chloride/methanol) gave alcohol **46** (4.8 g, 100%): <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 7.14 (dd, *J* = 8, 8 Hz, 1H), 7.00-6.92 (m, 2H), 4.44 (dd, *J* = 7, 7 Hz, 1H), 3.54-3.41 (m, 2H), 2.66 (dd, *J* = 8, 8 Hz, 2H), 2.16 (s, 3H), 1.67-1.62 (m, 2H).

**Step 4:** To an ice-cold, stirred solution of alcohol **46** (4.8 g, 29 mmol) in THF (150 mL) was added Et<sub>3</sub>N (5.8 mL, 42 mmol) and then methanesulfonyl chloride (2.7 mL, 34 mmol). The reaction mixture was stirred for 10 minutes and then diluted with EtOAc (300 mL). The organic layer was washed with 1N HCl (100 mL), H<sub>2</sub>O (100 mL), saturated NaHCO<sub>3</sub> (100 mL), saturated NaCl (100 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and filtered. Concentration under reduced pressure gave the desired mesylate **47** (7.5 g, 100%) which was used without further purification: <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 7.14 (dd, *J* = 8, 8 Hz, 1H), 7.02-6.95 (m, 2H), 4.23 (dd, *J* = 7, 6 Hz, 2H), 3.17 (s, 3H), 2.70 (dd, *J* = 8, 7 Hz, 2H), 2.17 (s, 3H), 1.94-1.88 (m, 2H).

**Step 5:** A mixture of mesylate **47** (7.1 g, 29 mmol), NaN<sub>3</sub> (2.8 g, 43 mmol), and tetrabutylammonium hydrogen sulfate (0.98 g, 2.9 mmol) in DMSO (50 mL) was heated to 45°C for 16 hours. After cooling, the reaction

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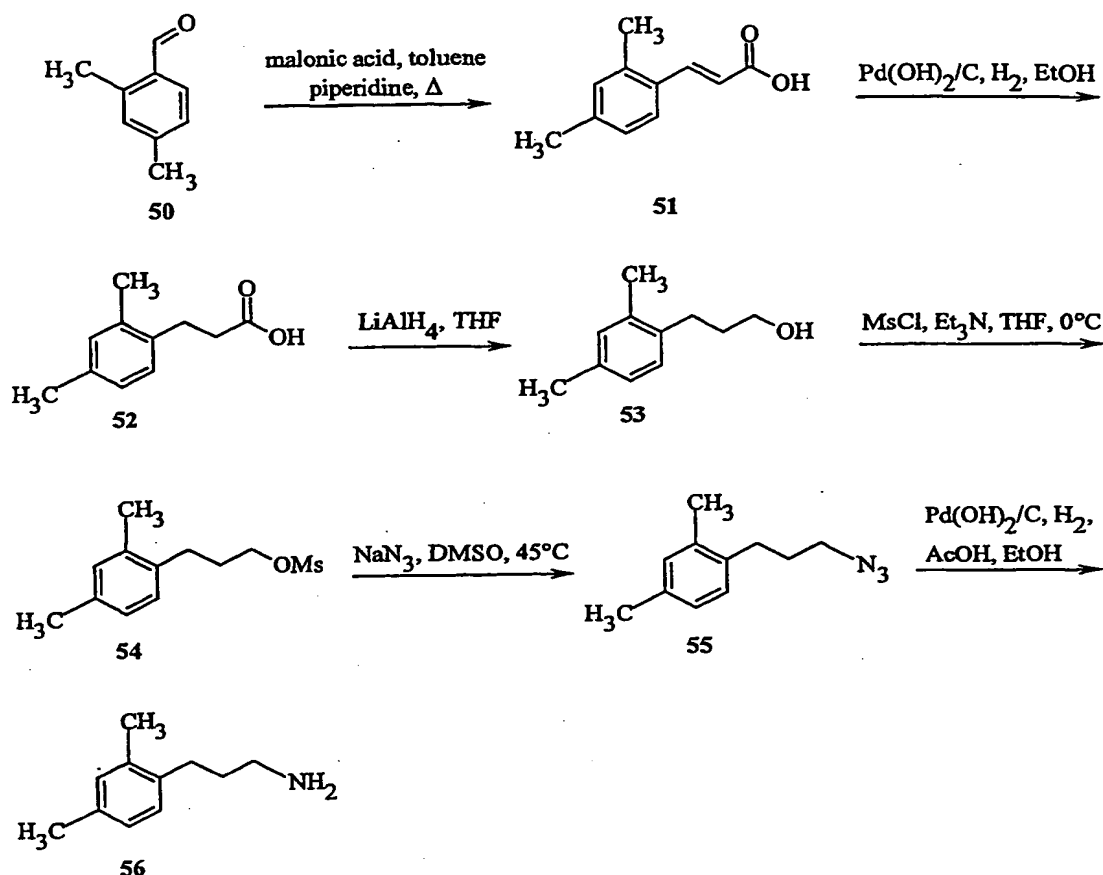
mixture was diluted with EtOAc (300 mL) and washed with H<sub>2</sub>O (3 × 100 mL), saturated NaCl (100 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 90:10 hexanes:EtOAc) gave azide 48 (3.9 g, 70%): <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 7.15 (dd, *J* = 8, 8 Hz, 1H), 7.00-6.96 (m, 2H), 3.37 (dd, *J* = 8, 7 Hz, 2H), 2.66 (dd, *J* = 8, 7 Hz, 2H), 2.17 (s, 3H), 1.79-1.73 (m, 2H).

**Step 6:** A mixture of azide 48 (3.9 g, 20 mmol), acetic acid (1.1 mL, 20 mmol), and 20% Pd(OH)<sub>2</sub>/C (150 mg) in EtOH (60 mL) was shaken under a H<sub>2</sub> atmosphere (balloon) for 30 hours. The solution was filtered through Celite and concentrated under reduced pressure. The residue was triturated with Et<sub>2</sub>O, and the resulting solid was collected by filtration to afford 3-(2-methyl-3-fluorophenyl)-1-propylamine 49 (2.3 g, 51%), as the AcOH salt: <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 7.14 (dd, *J* = 8, 8 Hz, 1H), 7.00-6.94 (m, 2H), 6.20 (br s, 3H), 2.67-2.62 (m, 4H), 2.16 (d, *J* = 2 Hz, 3H), 1.78 (s, 3H), 1.69-1.63 (m, 2H).

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## Scheme 9

## Preparation of 3-(2,4-Dimethylphenyl)-1-propylamine 56



**Step 1:** Reaction of 2,4-dimethylbenzaldehyde (10 g, 75 mmol), malonic acid (8.5 g, 82 mmol), piperidine (0.37 mL, 3.7 mmol), and toluene (150 mL), following the procedure described in the General Procedure, Scheme 8, Step 1, gave cinnamic acid **51** (6.5 g, 49%):  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.96 (d,  $J = 16$  Hz, 1H), 7.50 (d,  $J = 8$  Hz, 1H), 7.04-7.01 (m, 2H), 6.33 (d,  $J = 16$  Hz, 1H), 2.37 (s, 3H), 2.29 (s, 3H).

**Step 2:** Hydrogenation of cinnamic acid **51** (6.5 g, 37 mmol), following the procedure described in the General Procedure, Scheme 8, Step 2, gave acid **52** (6.6 g, 100%):  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.03-6.88 (m, 3H), 2.86 (dd,  $J = 8, 8$  Hz, 2H), 2.51 (dd,  $J = 8, 8$  Hz, 2H), 2.26 (s, 3H), 2.23 (s, 3H).

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**Step 3:** Reduction of acid **52** (6.6 g, 38 mmol) with  $\text{LiAlH}_4$  (1.4 g, 38 mmol), following the procedure described in the General Procedure, Scheme 8, Step 3, gave alcohol **53** (6.3 g, 100%):  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.00-6.86 (m, 3H), 3.57 (dd,  $J = 7, 7$  Hz, 2H), 2.61 (dd,  $J = 8, 8$  Hz, 2H), 2.25 (s, 3H),  
5 2.23 (s, 3H), 1.79-1.69 (m, 2H).

**Step 4:** Reaction of alcohol **53** (6.3 g, 38 mmol) with methanesulfonyl chloride (3.5 mL, 46 mmol), following the procedure described in the General Procedure, Scheme 8, Step 4, gave mesylate **54** (8.6 g, 93%):  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.01-6.90 (m, 3H), 4.23 (dd,  $J = 8, 8$  Hz, 2H), 3.04 (s, 3H),  
10 2.69 (dd,  $J = 8, 8$  Hz, 2H), 2.26 (s, 3H), 2.24 (s, 3H), 2.00-1.95 (m, 2H).

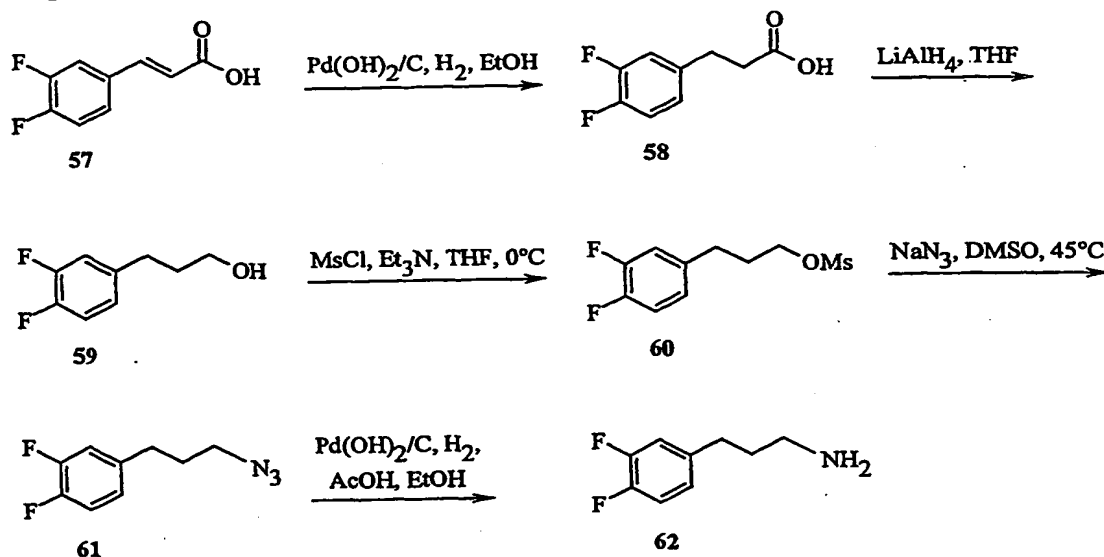
**Step 5:** Reaction of mesylate **54** (8.6 g, 35 mmol) with  $\text{NaN}_3$  (2.8 g, 43 mmol) in DMSO (40 mL), following the procedure described in the General Procedure, Scheme 8, Step 5, gave azide **55** (6.3 g, 95%):  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  6.98-6.89 (m, 3H), 3.31-3.28 (m, 2H), 2.64 (dd,  $J = 8, 8$  Hz, 2H),  
15 2.25 (s, 3H), 2.24 (s, 3H), 1.81-1.78 (m, 2H).

**Step 6:** Hydrogenation of azide **55** (3.4 g, 18 mmol), following the procedure described in the General Procedure, Scheme 8, Step 6, gave 3-(2,4-dimethylphenyl)-1-propylamine **56** (1.9 g, 47%), as the AcOH salt:  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.01 (d,  $J = 8$  Hz, 1H), 6.96 (s, 1H), 6.82 (d,  $J = 8$  Hz,  
20 1H), 2.95-2.91 (m, 2H), 2.66 (dd,  $J = 8, 8$  Hz, 2H), 2.27 (s, 3H), 2.24 (s, 3H), 1.88 (s, 3H), 1.89-1.87 (m, 2H).

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## Scheme 10

Preparation of 3-(3,4-Difluorophenyl)-1-propylamine 62



Step 1: Hydrogenation of cinnamic acid 57 (5.0 g, 27 mmol), following the procedure described in the General Procedure, Scheme 8, Step 2, gave acid 58 (5.0 g, 100%):  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.15-7.09 (m, 2H), 7.01-6.99 (m, 1H), 2.88 (dd,  $J = 8, 8$  Hz, 2H), 2.58 (dd,  $J = 8, 8$  Hz, 2H).

Step 2: Reduction of acid 58 (5.0 g, 27 mmol) with  $\text{LiAlH}_4$  (1.1 g, 29 mmol), following the procedure described in the General Procedure, Scheme 8, Step 3, gave alcohol 59 (3.2 g, 70%):  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.35-7.22 (m, 2H), 7.05-7.01 (m, 1H), 4.50 (br s, 1H), 3.39 (dd,  $J = 7, 7$  Hz, 2H), 2.60 (dd,  $J = 8, 8$  Hz, 2H), 1.74-1.64 (m, 2H).

Step 3: Reaction of alcohol 59 (8.1 g, 47 mmol) with methanesulfonyl chloride (4.4 mL, 56 mmol), following the procedure described in the General Procedure, Scheme 8, Step 4, gave mesylate 60 (11.5 g, 98%):  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.16-7.10 (m, 2H), 7.02-6.99 (m, 1H), 4.22 (dd,  $J = 8, 8$  Hz, 2H), 3.04 (s, 3H), 2.72 (dd,  $J = 8, 8$  Hz, 2H), 2.05-1.99 (m, 2H).

Step 4: Reaction of mesylate 60 (12 g, 50 mmol) with  $\text{NaN}_3$  (3.6 g, 55 mmol) in DMSO (60 mL), following the procedure described in the General Procedure, Scheme 8, Step 5, gave azide 61 (8.8 g, 89%):  $^1\text{H}$  NMR (500 MHz,

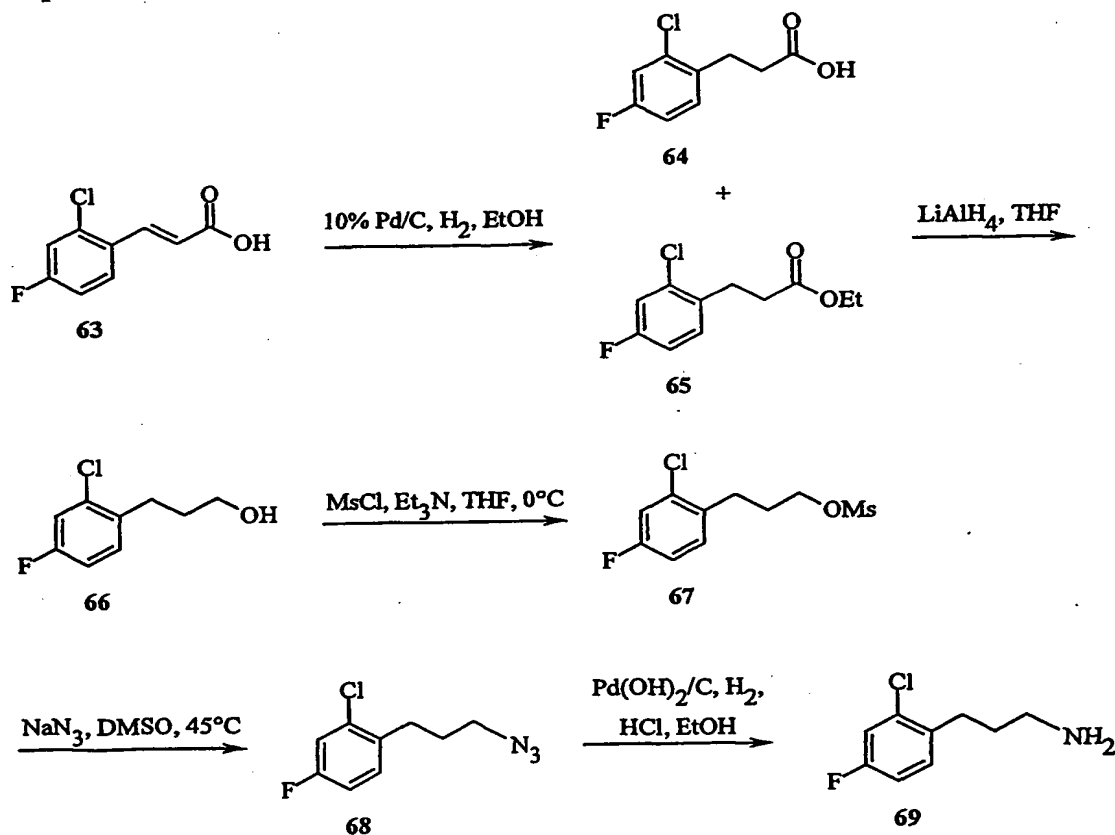


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CD<sub>3</sub>OD):  $\delta$  7.16-7.09 (m, 2H), 7.02-6.99 (m, 1H), 3.29 (dd,  $J = 8, 8$  Hz, 2H), 2.67 (dd,  $J = 8, 8$  Hz, 2H), 1.90-1.81 (m, 2H).

**Step 5:** Hydrogenation of azide **61** (8.8 g, 45 mmol), following the procedure described in the General Procedure, Scheme 8, Step 6, gave 3-(3,4-difluorophenyl)-1-propylamine **62** (1.9 g, 47%), which was converted to the HCl salt: <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>):  $\delta$  8.09 (br s, 3H), 7.37-7.29 (m, 2H), 7.09-7.06 (m, 1H), 2.75-2.72 (m, 2H), 2.66 (dd,  $J = 8, 8$  Hz, 2H), 1.89-1.83 (m, 2H).

## Scheme 11

Preparation of 3-(2-Chloro-4-fluorophenyl)-1-propylamine **69**

**Step 1:** Hydrogenation of cinnamic acid **63** (10 g, 52 mmol), following the procedure described in the General Procedure, Scheme 8, Step 2, except 10% Pd/C was used as catalyst, gave a mixture of acid **64** and ethyl ester **65** (11 g). Reduction of the mixture with LiAlH<sub>4</sub> (1.8 g, 48 mmol), following the procedure described in the General Procedure, Scheme 8, Step 3, gave alcohol **66** (9.7 g,

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100%):  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.30 (dd,  $J = 9, 7$  Hz, 1H), 7.20-7.14 (m, 1H), 7.00-6.96 (m, 1H), 3.58 (dd,  $J = 7, 7$  Hz, 2H), 2.78 (dd,  $J = 7, 7$  Hz, 2H), 1.84-1.78 (m, 2H).

5       **Step 2:** Reaction of alcohol 66 (9.1 g, 48 mmol) with methanesulfonyl chloride (4.5 mL, 58 mmol), following the procedure described in the General Procedure, Scheme 8, Step 4, gave mesylate 67 (13 g, 100%):  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.34 (dd,  $J = 7, 7$  Hz, 1H), 7.19 (dd,  $J = 9, 3$  Hz, 1H), 7.02 (ddd,  $J = 9, 7, 3$  Hz, 1H), 4.26 (dd,  $J = 7, 7$  Hz, 2H), 3.06 (s, 3H), 2.86 (dd,  $J = 8, 8$  Hz, 2H), 2.06-2.01 (m, 2H).

10       **Step 3:** Reaction of mesylate 67 (13 g, 49 mmol) with  $\text{NaN}_3$  (3.4 g, 53 mmol) in DMSO (50 mL), following the procedure described in the General Procedure, Scheme 8, Step 5, gave azide 68 (9.9 g, 96%):  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.32-7.28 (m, 1H), 7.21-7.16 (m, 1H), 7.02-6.97 (m, 1H), 3.33 (dd,  $J = 8, 8$  Hz, 2H), 2.82-2.79 (m, 2H), 1.90-1.83 (m, 2H).

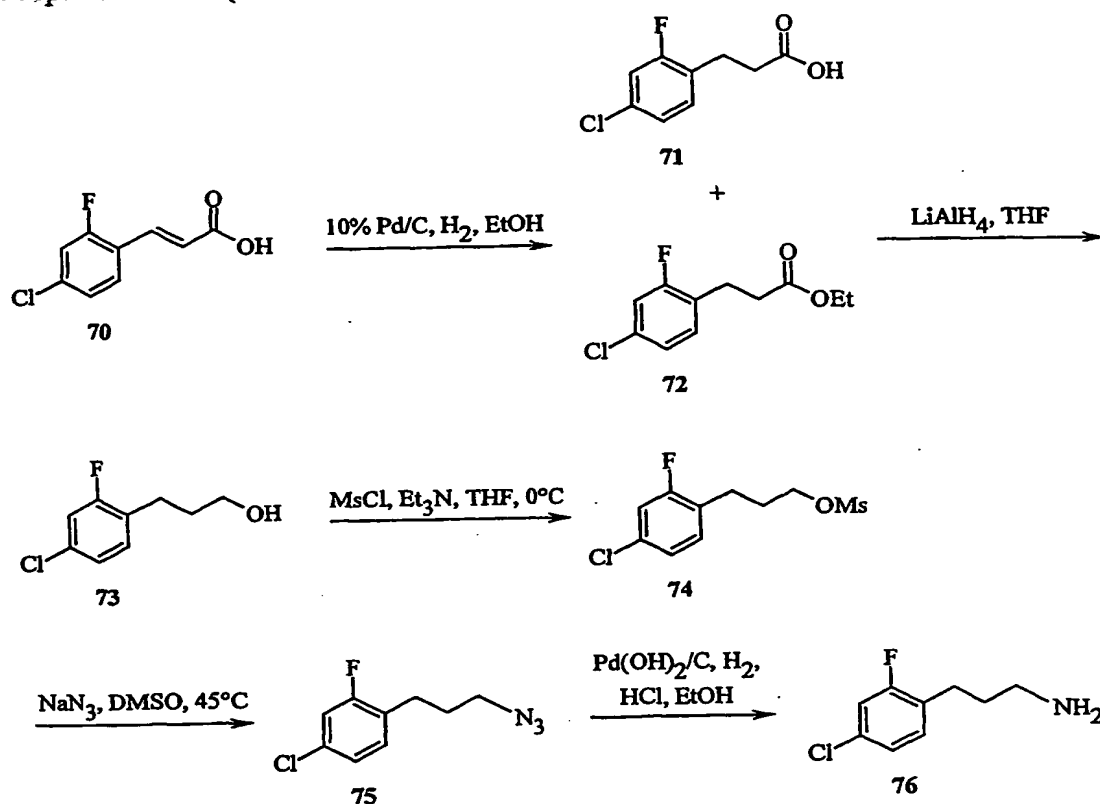
15       **Step 4:** Hydrogenation of azide 68 (10 g, 48 mmol), following the procedure described in the General Procedure, Scheme 8, Step 6, except HCl was used in place of AcOH, gave 3-(2-chloro-4-fluorophenyl)-1-propylamine 69 (7.8 g, 72%), as the HCl salt:  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.20 (br s, 3H), 7.45 (dd,  $J = 7, 7$  Hz, 1H), 7.40 (dd,  $J = 9, 3$  Hz, 1H), 7.19 (ddd,  $J = 9, 7, 3$  Hz, 1H), 2.84-2.74 (m, 4H), 1.91-1.84 (m, 2H).

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## Scheme 12

Preparation of 3-(4-Chloro-2-fluorophenyl)-1-propylamine 76



Step 1: Hydrogenation of cinnamic acid 70 (12 g, 60 mmol), following the procedure described in the General Procedure, Scheme 8, Step 2, except Pd/C was used, gave a mixture of acid 71 and ethyl ester 72 (12 g). Reduction of the mixture with LiAlH<sub>4</sub> (1.9 g, 50 mmol), following the procedure described in the General Procedure, Scheme 8, Step 3, gave alcohol 73 (9.4 g, 100%): <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD): δ 7.26-7.22 (m, 1H), 7.12-7.09 (m, 2H), 3.57 (dd, *J* = 7, 7 Hz, 2H), 2.70 (dd, *J* = 7, 7 Hz, 2H), 1.84-1.77 (m, 2H).

Step 2: Reaction of alcohol 73 (9.4 g, 50 mmol) with methanesulfonyl chloride (4.6 mL, 60 mmol), following the procedure described in the General Procedure, Scheme 8, Step 4, gave mesylate 74 (13 g, 100%): <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD): δ 7.28 (dd, *J* = 7, 7 Hz, 1H), 7.15-7.13 (m, 2H), 4.24 (dd, *J* = 7, 7 Hz, 2H), 3.06 (s, 3H), 2.77 (dd, *J* = 8, 8 Hz, 2H), 2.06-2.00 (m, 2H).

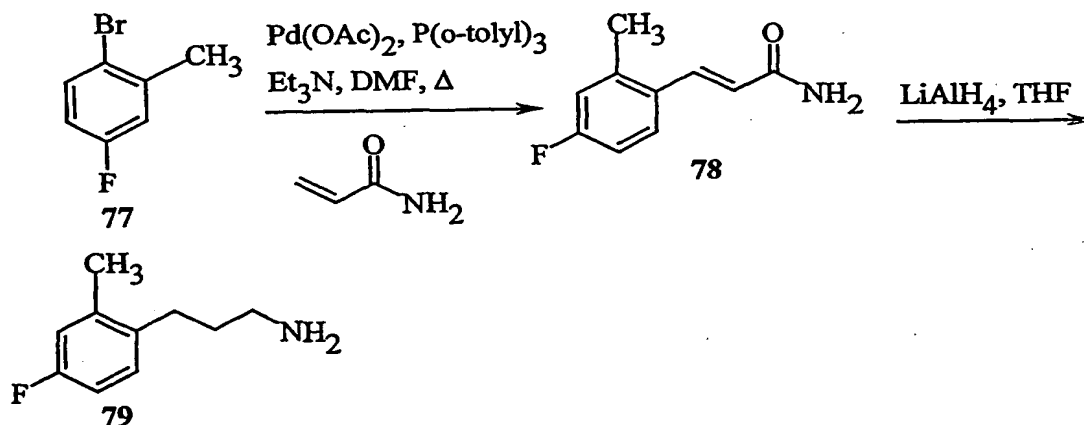
Step 3: Reaction of mesylate 74 (13 g, 50 mmol) with NaN<sub>3</sub> (3.6 g, 55 mmol) in DMSO (50 mL), following the procedure described in the General

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Procedure, Scheme 8, Step 5, gave azide **75** (11 g, 96%):  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.26-7.22 (m, 1H), 7.14-7.09 (m, 2H), 3.31 (dd,  $J = 7, 7$  Hz, 2H), 2.70 (dd,  $J = 7, 7$  Hz, 2H), 1.90-1.83 (m, 2H).

**Step 4:** Hydrogenation of azide **75** (11 g, 50 mmol), following the procedure described in the General Procedure, Scheme 8, Step 6, except HCl was used in place of AcOH, gave 3-(4-chloro-2-fluorophenyl)-1-propylamine **76** (7.4 g, 66%), as the HCl salt:  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  8.18 (br s, 3H), 7.41-7.36 (m, 2H), 7.26-7.31 (m, 1H), 2.84-2.77 (m, 2H), 2.69 (dd,  $J = 8, 8$  Hz, 2H), 1.90-1.83 (m, 2H).

## Scheme 13

Preparation of 3-(4-Fluoro-2-methylphenyl)-1-propylamine **79**

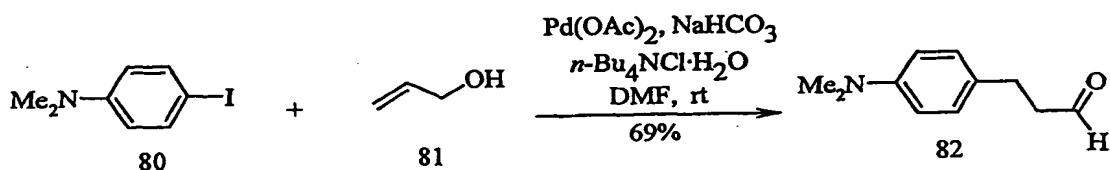
**Step 1:** A mixture of 2-bromo-5-fluorotoluene (2.0 g, 11 mmol), acrylamide (1.5 g, 21 mmol),  $\text{P}(o\text{-tolyl})_3$  (320 mg, 1.1 mmol), and  $\text{Et}_3\text{N}$  (2.9 mL, 21 mmol), in toluene (25 mL) was deoxygenated by bubbling a stream of Ar through the solution for 15 minutes. Palladium(II) acetate (120 mg, 0.53 mmol) was added to the reaction mixture, and a stream of Ar was again passed through the mixture for 15 minutes. The reaction was heated to  $140^\circ\text{C}$  for 2.25 hours, then cooled to ambient temperature, diluted with  $\text{EtOAc}$ , and filtered through Celite. The filtrate was washed with  $\text{H}_2\text{O}$ , 1N HCl,  $\text{H}_2\text{O}$ , dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated under reduced pressure to give amide **78** (1.7 g, 86%) which was used without further purification:  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  7.60-7.52 (m, 3H), 7.15-7.04 (m, 3H), 6.46 (d,  $J = 16$  Hz, 1H), 2.37 (s, 3H).

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Step 2: To amide 78 (2.3 g, 13 mmol) in THF (25 mL) was added LiAlH<sub>4</sub> 970 mg, 25 mmol) portionwise over 5 minutes. The reaction mixture was heated to reflux for 1 hour, cooled in an ice/H<sub>2</sub>O bath, carefully quenched with methanol, filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (silica, 90:9.5:0.5 methylene chloride:methanol:NH<sub>4</sub>OH) gave 3-(4-fluoro-2-methylphenyl)-1-propylamine 79 (580 mg, 22%), as the HCl salt: <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 8.05 (br s, 3H), 7.20-7.14 (m, 1H), 7.03-6.91 (m, 2H), 2.80 (dd, *J* = 8, 6 Hz, 2H), 2.63 (dd, *J* = 8, 8 Hz, 2H), 2.29 (s, 3H), 1.88-1.76 (m, 2H).

## Scheme 14

Preparation of 3-(4-Dimethylaminophenyl)propionaldehyde 82

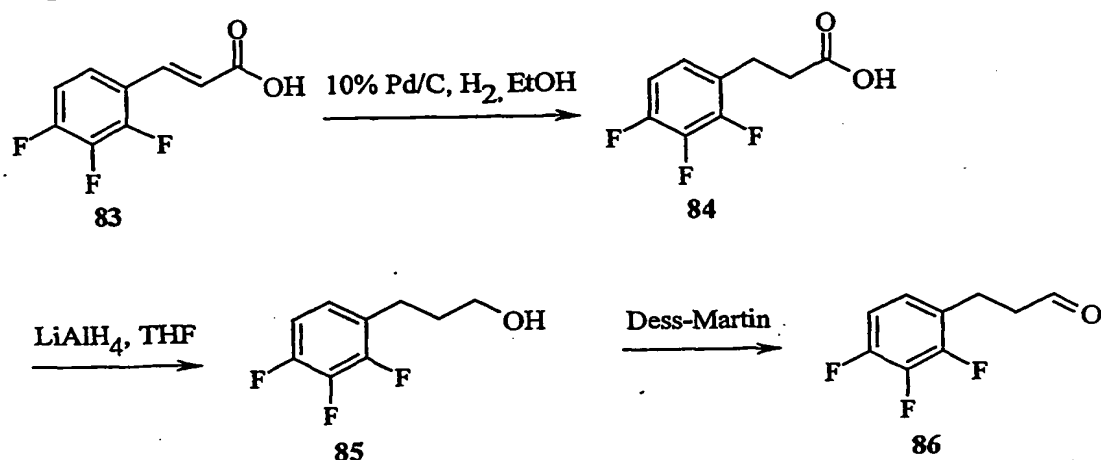


Alcohol 81 (2.80 mL, 56.5 mmol), (4-iodophenyl)dimethylamine 80 (5.04 g, 20.4 mmol), sodium bicarbonate (4.30 g, 51.2 mmol), and tetrabutylammonium chloride hydrate (5.68 g, 20.4 mmol) were combined in DMF (25 mL). The reaction mixture was deoxygenated by passing a stream of argon through the solution for 15 minutes. Palladium(II) acetate (59 mg, 0.24 mmol) was added, and a stream of argon was again bubbled through the mixture for 10 minutes. After stirring under an argon atmosphere for 62 hours, the reaction mixture was partitioned between EtOAc (300 mL) and water (200 mL). The organic layer was separated, washed with water (3 × 200 mL) and saturated NaCl (200 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure. Purification by chromatography (silica, 9:1 to 3:2 hexanes:EtOAc) gave 3-(4-dimethylaminophenyl)propionaldehyde 82 (910 mg, 25%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 9.82 (s, 1H), 7.08 (d, *J* = 8 Hz, 2H), 6.70 (d, *J* = 8 Hz, 2H), 2.91 (s, 6H), 2.90-2.85 (m, 2H), 2.73 (dd, *J* = 8, 7 Hz, 2H).

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## Scheme 15

Preparation of 3-(2,3,4-Trifluorophenyl)propionaldehyde 86



5        **Step 1:** Hydrogenation of cinnamic acid 83 (5.0 g, 25 mmol), following the procedure described in the General Procedure, Scheme 8, Step 2, except 10% Pd/C was used, gave acid 84 (5.0 g, 99%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.25-7.14 (m, 2H), 2.85 (dd, *J* = 8, 7 Hz, 2H), 2.54 (dd, *J* = 8, 7 Hz, 2H).

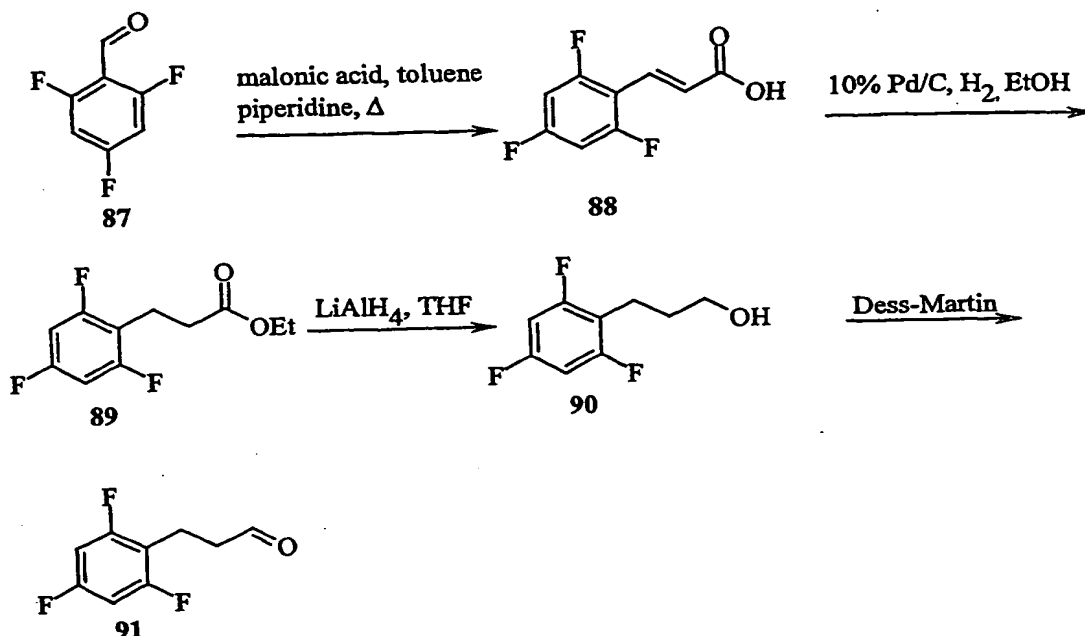
10        **Step 2:** Reduction of acid 84 (5.0 g, 24 mmol) with LiAlH<sub>4</sub> (930 mg, 24 mmol), following the procedure described in the General Procedure, Scheme 8, Step 3, gave alcohol 85 (4.6 g, 100%): <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 7.23-7.11 (m, 2H), 4.45 (t, *J* = 5 Hz, 1H), 3.42 (dd, *J* = 6, 6 Hz, 2H), 2.66 (dd, *J* = 8, 8 Hz, 2H), 1.70-1.63 (m, 2H).

15        **Step 3:** A mixture of alcohol 85 (1.0 g, 5.3 mmol), Dess-Martin periodane (4.5 g, 11.0 mmol), and water (0.1 mL) in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was stirred for 4 hours. The reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (40 mL), filtered through Celite, and the resulting filtrate concentrated under reduced pressure. Purification by chromatography (silica, 9:1 hexanes:EtOAc) gave 3-(2,3,4-trifluorophenyl)-propionaldehyde 86 (280 mg, 28%) as an oil: <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 9.71 (s, 1H), 7.34-7.17 (m, 2H), 2.89-2.81 (m, 4H).

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## Scheme 16

Preparation of 3-(2,4,6-Trifluorophenyl)propionaldehyde 91



Step 1: Reaction of 2,4,6-trifluorobenzaldehyde (4.7 g, 29 mmol), malonic acid (3.4 g, 32 mmol), piperidine (0.14 mL, 1.4 mmol), and toluene (75 mL), following the procedure described in the General Procedure, Scheme 8, Step 1, gave cinnamic acid 88 (2.2 g, 37%):  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  7.80 (dd,  $J = 16$  Hz, 1H), 6.79-6.65 (m, 3H), 6.97 (dd,  $J = 8, 8$  Hz, 1H).

Step 2: Hydrogenation of cinnamic acid 88 (2.2 g, 11 mmol), following the procedure described in the General Procedure, Scheme 8, Step 2, except 10% Pd/C was used, gave ethyl ester 89 (2.2 g, 88%):  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  6.72-6.62 (m, 2H), 3.73 (q,  $J = 14, 7$  Hz, 2H), 3.02-2.94 (m, 2H), 2.64 (dd,  $J = 7, 7$  Hz, 2H), 1.25 (t,  $J = 7$  Hz, 3H).

Step 3: Reduction of ester 89 (2.2 g, 11 mmol) with  $LiAlH_4$  (410 mg, 11 mmol), following the procedure described in the General Procedure, Scheme 8, Step 3, gave alcohol 90 (470 mg, 26%):  $^1H$  NMR (500 MHz,  $DMSO-d_6$ ):  $\delta$  7.19-7.07 (m, 2H), 4.47 (t,  $J = 5$  Hz, 1H), 6.83 (dd,  $J = 8, 6$  Hz, 2H), 2.61 (dd,  $J = 8, 8$  Hz, 2H), 1.66-1.61 (m, 2H).

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Step 4: A mixture of alcohol **90** (470 mg, 2.50 mmol), Dess-Martin periodane (2.1 g, 4.90 mmol), and water (0.04 mL) in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) was stirred for 3 hours. The reaction mixture was filtered through Celite and the resulting filtrate concentrated under reduced pressure. Purification by chromatography (silica, 5:1 hexanes:EtOAc) gave 3-(2,4,6-trifluorophenyl)-propionaldehyde **91** (360 mg, 76%) as an oil: <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>): δ 9.67 (s, 1H), 7.22-7.13 (m, 2H), 2.82-2.80 (m, 2H), 2.75-2.72 (m, 2H).

#### Electrophysiological Assays at NMDA Receptor Subunits

Preparation of RNA. cDNA clones encoding the NR1A, NR2A, NR2B, and NR2C rat NMDA receptor subtypes were used (see, Moriyoshi, supra., 1991; Kutsuwada et al., supra., 1992; Monyer et al., supra., 1992; Ikeda et al., *FEBS Lett.*, 1992;313:34-38; Ishii et al., *J. Biol. Chem.*, 1993;268:2836-2843 for details of these clones or their mouse homologs). The clones were transformed into appropriate host bacteria and plasmid preparations were made with conventional DNA purification techniques. A sample of each clone linearized by restriction enzyme digestion of cRNA was synthesized with T3 RNA polymerase. The cRNA was diluted to 400 ng/μL and stored in 1-μL aliquots at -80°C until injection.

The *Xenopus* oocyte expression system. Mature female *Xenopus laevis* were anaesthetized (20-40 minutes) using 0.15% 3-aminobenzoic acid ethyl ester (MS-222), and 2 to 4 ovarian lobes were surgically removed. Oocytes at developmental stages IV-VI (Dumont J.N., *J. Morphol.*, 1972;136:153-180) were dissected from the ovary still surrounded by enveloping ovarian tissues. Follicle-enclosed oocytes were microinjected with 1:1 mixtures of NR1A:NR2A, 2B or 2C; injecting 1 to 10 ng of RNA encoding each receptor subunit. NR1A encoding RNA was injected alone at ~20 ng. Oocytes were stored in Barth's medium containing (in mM): NaCl, 88; KCl, 1; CaCl<sub>2</sub>, 0.41; Ca (NO<sub>3</sub>)<sub>2</sub>, 0.33; MgSO<sub>4</sub>, 0.82; NaHCO<sub>3</sub>, 2.4; HEPES 5; pH 7.4, with 0.11 mg/mL gentamicin sulphate. While oocytes were still surrounded by enveloping ovarian tissues, the Barth's medium was supplemented with 0.1% bovine serum. Oocytes were defolliculated 1 to 2 days following injections by treatment with collagenase (0.5 mg/mL Sigma



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Type I for 0.5-1 hr) – (Miledi and Woodward, *J. Physiol., (Lond.)* 1989;416:601-621) and subsequently stored in serum-free medium.

Electrical recordings were made using a conventional two-electrode voltage clamp (Dagan TEV-200) over periods ranging between 3 to 21 days following injection (Woodward et al., *Mol. Pharmacol.*, 1992;41:89-103). Oocytes were placed in a 0.1-mL recording chamber continuously perfused (5 mL-15 mL min<sup>-1</sup>) with frog Ringer's solution containing (in mM): NaCl, 115; KCL, 2; BaCl<sub>2</sub>, 1.8; HEPES, 5; and pH 7.4. Drugs were applied by bath perfusion. Using oocytes expressing different subunit combinations of NMDA receptor, NMDA currents were activated by co-application of glutamate (100 μM) and glycine (1 -100 μM). Inhibitory potency of the novel antagonists was assessed on responses elicited by fixed concentrations of glutamate and glycine, by measuring reductions in current induced by progressively increasing concentrations of antagonist.

Concentration-inhibition curves were fit with Equation 1.

$$I/I_{\text{control}} = 1/(1 + ([\text{antagonist}]/10^{-\text{pIC}_{50}})^n) \quad \text{Eq. 1}$$

In which  $I_{\text{control}}$  is the current evoked by agonists alone,  $\text{pIC}_{50} = -\log \text{IC}_{50}$ ,  $\text{IC}_{50}$  is the concentration of antagonist that produced half maximal inhibition, and  $n$  is the slope factor (De Lean et al., *Am. J. Physiol.*, 1978;235:E97-102). For incomplete curves, analysis by fitting was unreliable and  $\text{IC}_{50}$  values were calculated by simple regression over linear portions of the curves (Origin: Microcal Software).

The electrophysiological assay results are set forth in Table 1.

#### 6-OHDA Lesioned Rat Assay:

6-Hydroxydopamine-lesioned rats were used (see Ungerstedt U., Arbuthnott G.W., Quantitative recording of rotational behavior in rats after 6-hydroxy-dopamine lesions of the nigrostriatal dopamine system. *Brain Res.*, 1971;24(3):485-93). Adult male Sprague-Dawley rats were anesthetized with chloral hydrate and unilateral lesions of the nigrostriatal dopamine system were

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accomplished by infusion of 8  $\mu$ g of 6-hydroxydopamine HBr (6-OHDA) into the right medial forebrain bundle. Rats were pretreated 30 minutes before surgery with desipramine HCl 25 mg/kg intraperitoneally (IP) to protect noradrenergic neurons, and pargyline 25 mg/kg IP to potentiate the effects of 6-OHDA. A minimum of 3 weeks after surgery, the rotational behavior induced by apomorphine HCl 50  $\mu$ g/kg subcutaneously (SC) was assessed. Only rats demonstrating more than 100 contraversive turns/hour to apomorphine were used for the present experiments.

Rotational behavior was measured using an automatic rotometer system (Rotorat Rotational Activity System, MED Associates, Georgia, Vermont). Anti-parkinsonian activity was assessed as the ability of the compound to potentiate the contraversive rotation induced by L-DOPA methyl ester, 10 mg/kg SC, over a 6-hour period. Experiments were conducted using a crossover paradigm where each rat received either a vehicle plus L-DOPA, or the test compound plus L-DOPA, in randomized order. Rats were tested at 7-day intervals. In experiments in which the compound was tested orally, rats were food deprived for 16 hours. Statistical analysis between treatment groups were performed using a paired t-test. The results were reported in Table 1 as the minimum effective dose (MED) of compound (mg/kg) required to produce a statistically-significant increase in total contraversive rotations compared to rats receiving L-DOPA only.

#### [<sup>3</sup>H]Ifenprodil Binding Assay Protocol:

### MATERIALS and METHODS

All buffers and reagents used in assay incubations or to dissolve drugs were prepared using water purified through a Milli-Q reverse osmosis system (Millipore Corp, Bedford, Massachusetts) and treated with UV emissions. Prior to use in the assays, buffers were further filtered through a sterile Corning filtration unit (Corning Glass Works, Corning, New York) containing a 0.2-micron filter. Buffer used to rinse the membranes on the assay filters was prepared with purified water, but was not refiltered and was stored no longer than 5 days. Stock solutions of the drugs (usually 10 mM) were dissolved in 20 mM HEPES-KOH buffer

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pH 7.4 (assay buffer) with the addition of 1 to 5  $\mu$ L of glacial AcOH, if needed to keep them in solution. For eliprodil the stock solution was buffered with the addition of 10% DMSO. All subsequent dilutions from stock were made in buffer.

#### Membrane Preparation

5           An extensively washed buffy coat membrane fraction was prepared from frozen adult rat forebrains (Zivic-Miller Laboratories, Inc., Zelienople, Pennsylvania) as described previously (Coughenour L.L., Cordon, J.J., *J. Pharmacol. Exp. Ther.*, 1997;280:584-592) and stored at  $-80^{\circ}\text{C}$ . On the day of the assay, pellets were resuspended in 35 mL of assay buffer at pH 7.4 using a  
10       Polytron setting 6. After incubation at  $37^{\circ}\text{C}$  for 30 minutes in a shaking water bath, the homogenate was centrifuged  $40,000 \times g$  for 10 minutes at  $4^{\circ}\text{C}$ . The pellets were resuspended in fresh buffer and centrifuged 3 more times before final suspension for use in the assay.

#### Binding Studies

15           [ $^3\text{H}$ ]Ifenprodil Binding. Triplicate incubations were carried out in a volume of 0.5 mL in 1.3 mL polypropylene tubes (Marsh Biomedical Products Inc., Rochester, New York) for 2 hours at room temperature. Incubations contained test agents, membranes (100-200  $\mu\text{g}$  protein) and 4 nM [ $^3\text{H}$ ]-ifenprodil in 20 mM HEPES-KOH buffer, pH 7.4 (assay buffer). Assays were started by  
20       addition of the membranes. Bound radioligand was separated by filtration under reduced pressure using a Tomtec Mach II, 96-well cell harvester (Tomtec Inc., Orange, Colorado). Filtration was through Whatman GF/B glass fiber filters (Whatman Ltd, Maidstone, England), which had been soaked for at least  
25       15 minutes in 0.3% polyethylenimine and allowed to air dry. The filters were rinsed with 3 mL of ice cold assay buffer within 6 seconds. Air was allowed to pass through the filters for an additional 10 seconds to remove residual moisture. The filter mat was supported on a cold ( $-20^{\circ}\text{C}$ ) teflon support, and filters from individual wells were separated and placed in Mini Poly-Q vials (Beckman Instruments Inc., Fullerton, California) and filled with 4 mL of scintillation  
30       cocktail (Beckman Ready Protein<sup>+</sup>). Radioactivity retained on the filter was determined by liquid scintillation spectrophotometry. Nonspecific binding was

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defined as the binding in the presence of 1 mM ifenprodil. Specific binding was 90%.

**[<sup>3</sup>H]-TCP binding.** Binding assays were carried out essentially as described for [<sup>3</sup>H]ifenprodil binding. Incubations contained test agents, 100 to 200 µg protein, 2 nM [<sup>3</sup>H]-TCP, and 10 µM glutamate, glycine and spermidine. Incubations were for 10 minutes to allow assays to be carried out under nonequilibrium conditions for the detection of binding selective to NMDA receptors of the NR2B subtype. Specific binding was defined as the binding displaced by 100 µM (+)MK-801 and was 90% of the total binding.

**Data analysis.** Binding curves were statistically analyzed for a best one or two site competition fit using GraphPad Prism software (GraphPad Software Inc., San Diego, California). The normalized data was fit by nonweighted nonlinear regression to either

$$y = \text{Bottom} + \frac{(\text{Top}-\text{Bottom})}{1 + 10^{x-\text{LogEC50}}}$$

or

$$y = \text{Bottom} + (\text{Top}-\text{Bottom}) \frac{\text{Fraction}-1}{1 + 10^{x-\text{LogEC50}_1}} + \frac{1-\text{Fraction}-1}{1 + 10^{x-\text{LogEC50}_2}}$$

Control data was entered as 100%, and no parameters were constrained. Inhibition curves were compared by ANOVA with post test comparisons of the logIC<sub>50</sub> using Dunnett's multiple comparisons post test or Student's nonpaired, two-tailed t-test (GraphPad InStat software).

**Materials.** TCP, [piperidyl-3,4-<sup>3</sup>H(N)]- (specific activity, 45-50 Ci/mmol) and ifenprodil, [phenyl-<sup>3</sup>H]- (specific activity, 66.2 Ci/mmol) were purchased from Dupont NEN Research Products (Boston, Massachusetts). Ifenprodil tartrate, trifluoperidol hydrochloride, and GBR-12909 dihydrochloride were purchased from Research Biochemicals International (Natick, Massachusetts). Spermidine trihydrochloride was purchased from United States Biochemical Corp (Cleveland, Ohio). HEPES, glutamate, and glycine were purchased from Sigma Chemical Co, (St. Louis, Missouri). Haloperidol was obtained from McNeil Laboratories

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(Raritan, New Jersey) or Research Biochemicals International. Eliprodil was synthesized by Thomas Malone (Parke-Davis Pharmaceutical Research, Ann Arbor, Michigan), and (+)MK-801 was synthesized by Leonard Lescosky (Parke-Davis Pharmaceutical Research, Ann Arbor, Michigan).

5

TABLE 1

Example	NR1A/NR2B	[ <sup>3</sup> H]Ifenprodil	6-OHDA
	Oocyte	IC <sub>50</sub>	MED
	IC <sub>50</sub> (μM)	(μM)	(mg/kg)
1	0.03	0.004	30 (active)
2	0.10	0.040	10.0 (active)
3	0.10	0.034	10.0 (active)
4a	0.02	0.007	10.0 (inactive)
5a	0.02	0.004	
5b		0.021	
6		0.009	
7	0.09	0.037	
8	0.02		
9	0.06	0.015	
10	0.11	0.049	
11a	55.00	>1	
11b	10	>1	
12	70	22.5	
13a	0.08	0.038	
13b	0.02	0.005	
14		0.128	

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TABLE 1 (cont'd)

Example	NR1A/NR2B	[ <sup>3</sup> H]Ifenprodil	6-OHDA
	Oocyte	IC <sub>50</sub>	MED
	IC <sub>50</sub> (μM)	(μM)	(mg/kg)
15	0.46	0.092	
16	2.50	1.730	
17		0.010	10 (active)
18	0.065	0.009	10 (active)
19		0.185	
20		0.025	30 (active)
21		0.016	10 (active)
22		0.053	10 (active)
23		0.038	10 (active)
24b		0.014	
25		0.079	10 (active)
26		0.188	
27		0.132	
28		0.184	
29		0.018	
30		0.219	
31		0.465	
32		0.158	
33		>1 μM	
34		0.152	
35		0.170	
36b		>1 μM	

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TABLE 1 (cont'd)

Example	NR1A/NR2B	[ <sup>3</sup> H]Ifenprodil	6-OHDA
	Oocyte	IC <sub>50</sub>	MED
	IC <sub>50</sub> (μM)	(μM)	(mg/kg)
37b		0.032	
38b		0.007	
39b		0.037	
40b		0.029	
41b		0.068	
42b		0.980	
43b		0.056	
44b		0.007	
45b		0.007	
46b		0.009	
47b		0.015	
48b		0.020	
49b		0.022	
50b		0.351	
51b		0.550	
52b		0.003	
53		0.002	
54		0.034	
55		0.005	
56		0.071	
57		0.006	
58		0.357	

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TABLE 1 (cont'd)

Example	NR1A/NR2B	[ <sup>3</sup> H]Ifenprodil	6-OHDA
	Oocyte	IC <sub>50</sub>	MED
	IC <sub>50</sub> (μM)	(μM)	(mg/kg)
59		0.316	
60		>1 μM	
61b		0.012	
62		0.017	
63		0.002	
64		0.045	
65		0.067	

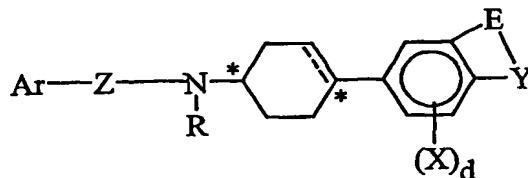
While the forms of the invention exemplified herein such as, for example, the named species of Formulas I-III and the recitation of treatment of Parkinson's constitute presently preferred embodiments, many others are possible. It is not intended that said recited species of Formulas I-III and preferred methods of use should, in any manner, limit or restrict the invention from the full scope claimed herein. It is not intended herein to name all of the possible equivalent forms or ramifications of the invention. It is understood that the terms used herein are merely descriptive, rather than limiting. For example, the term "Parkinson's disease" is merely descriptive, and not limiting, of the term "neurodegenerative disease."



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CLAIMS

What is claimed is:

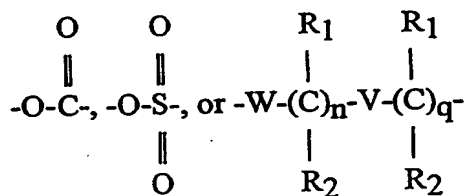
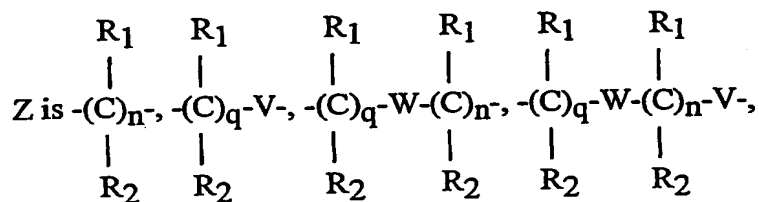
1. Bicycle-substituted cyclohexyl amines of Formula 1 and their pharmaceutically acceptable salts thereof



I

wherein:

Ar is substituted 1 to 3 times or unsubstituted aryl or substituted 1 to 3 times or unsubstituted heteroaryl, which heteroaryl is from 5 to 14 atoms having from 1 to 2 heteroatoms selected from N, O, and S wherein the substituents are selected from the groups F, Cl, Br, I, OH, NH<sub>2</sub>, SH, CN, NO<sub>2</sub>, OCH<sub>3</sub>, OC(O)CH<sub>3</sub>, CF<sub>3</sub>, OCH<sub>2</sub>CH<sub>2</sub>OH, NHC(O)CH<sub>3</sub>, NHCH<sub>3</sub>, or N(CH<sub>3</sub>)<sub>2</sub>;



wherein V is  $-(CH_2)_n-$ ,  $-C-$ ,  $-S(O)-$ , or  $-S(O)_2-$ ,

W is  $-(CH_2)_n-$ ,  $-C-$ ,  $-S(O)-$ ,  $-S(O)_2-$ ,  $-O-$ ,  $-S-$ ,  $-C\equiv C-$ , or *entgegen* or *zusammen*  $-CH(R_1)=CH(R_2)-$ ,

d is an integer from 0 to 2;

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n is an integer from 1 to 6;

q is an integer from 0 to 6;

R<sub>1</sub> and R<sub>2</sub> are independently selected from the group consisting of

hydrogen, alkyl, OH, hydroxyalkyl, aminoalkyl, aralkyl, or

N(R<sub>4</sub>)(R<sub>5</sub>) wherein R<sub>4</sub> and R<sub>5</sub> are independently selected from

hydrogen, alkyl, aralkyl, heteroaryl, heteroaralkyl, aminoalkyl,

hydroxyalkyl, and thioalkyl;

R is hydrogen, alkyl, C(O)R<sub>6</sub>, C(O)OR<sub>6</sub>, C(O)NHR<sub>6</sub>, -alkyl-C(O)NH<sub>2</sub>,

aralkyl, (C<sub>3</sub>-C<sub>7</sub> cycloalkyl)-alkyl, hydroxyalkyl, aminoalkyl,

amino(hydroxy)alkyl, carboxyalkyl, heteroaralkyl, alkenylalkyl, or

OH wherein R<sub>6</sub> is alkyl or aralkyl;

X is independently selected from hydrogen or an electron withdrawing group;

-E-Y- is -CH=CH-N(H)-;

-(CH<sub>2</sub>)<sub>2</sub>-N(H)-,

-CH=N-N(H)-,

-C(O)-CH<sub>2</sub>-N(H)-,

-CH<sub>2</sub>-C(O)-N(H)-,

-CH<sub>2</sub>-S(O)-N(H)-,

-CH<sub>2</sub>-S(O)<sub>2</sub>-N(H)-,

-CH=CH-CH(OH)-,

-(CH<sub>2</sub>)<sub>2</sub>-CH(OH)-,

-C(O)-CH<sub>2</sub>-C(O)-,

-C(O)-NH-C(O)-,

-N=CH-N(H)-,

-N(H)-C(O)-N(H)-,

-O-C(O)-NH-,

-S-C(O)-NH-,

-O-N=CH(OH)-,

-S-N=CH(OH)-,

-N=N-N(H)-,

-CH=CH-CH=C(OH)-,

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-(CH<sub>2</sub>)<sub>3</sub>-CH(OH)-,  
 -(CH<sub>2</sub>)<sub>2</sub>-S(O)-N(H)-,  
 -(CH<sub>2</sub>)<sub>2</sub>-S(O)<sub>2</sub>-N(H)-,  
 -CH=CH-C(O)-N(H)-,  
 5 -C(O)-NH-N=C(OH)-,  
 -CH=N-NH-C(O)-,  
 -CH=N(O)-N=C(OH)-,  
 -N(H)-C(O)-N(H)-C(O)-,  
 -N=CH-C(O)-NH-,  
 10 -O-CH<sub>2</sub>-C(O)-NH-,  
 -S-CH<sub>2</sub>-C(O)-NH-, or  
 -N(H)-C(O)-C(O)-N(H)-,

—denotes a single or double bond; and

\* denotes *cis* or *trans* or a mixture thereof.

- 15 2. A compound according to Claim 1 wherein:  
 X is independently selected from hydrogen or an electron withdrawing  
 group selected from the group consisting of halogen, nitro, cyano,  
 aminoalkyl CF<sub>3</sub>, C(O)CH<sub>3</sub>, and haloalkyl.

- 20 3. A compound of Claim 1 wherein:  
 Ar is unsubstituted or substituted phenyl;  
 X is independently selected from hydrogen or an electron withdrawing  
 group selected from the group consisting of halogen, nitro, cyano,  
 aminoalkyl, CF<sub>3</sub>, C(O)CH<sub>3</sub>, and haloalkyl;

25 -E-Y- is selected from  $\text{-O-C(=O)-NH-}$ ,  $\text{-S-C(=O)-NH-}$ ,  $\text{-CH=CH-NH-}$ ,  $\text{-N=CH-NH-}$ ,  
 $\text{-NH-C(=O)-NH-}$ ,  $\text{-N=N-NH-}$ , and  $\text{-NH-C(=O)-C(=O)-NH-}$ ; and

30

\* denotes *trans*.

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4. A compound according to Claim 1 wherein:

Ar is unsubstituted or substituted phenyl;

Z is a group whereby Ar and the nitrogen atom in Formula I are separated by from 2 to 4 atoms;

- 5 X is independently selected from hydrogen or an electron withdrawing group selected from the group consisting of halogen, nitro, cyano, aminoalkyl,  $\text{CF}_3$ ,  $\text{C}(\text{O})\text{CH}_3$ , and haloalkyl;

10 -E-Y- is selected from  $\text{-O-C(=O)-NH-}$ ,  $\text{-S-C(=O)-NH-}$ ,  $\text{-CH=CH-NH-}$ ,  $\text{-N=CH-NH-}$ ,  
 $\text{-NH-C(=O)-NH-}$ ,  $\text{-N=N-NH-}$ , and  $\text{-NH-C(=O)-C(=O)-NH-}$ ; and  
 \* denotes *trans*.

- 15 5. A compound according to Claim 1 wherein:

Ar is unsubstituted or substituted phenyl;

20 Z is  $\text{-CH}_2\text{-(CH}_2\text{)}_m\text{-}$ ,  $\text{-(CH}_2\text{)}_m\text{-C(=O)-}$ ,  $\text{-O-(CH}_2\text{)}_m\text{-}$ ,  $\text{-(CH}_2\text{)}_m\text{-CH(CH}_3\text{)-}$ ,  
 $\text{-(CH}_2\text{)}_m\text{-CH(OH)-H}_2\text{-}$ ,  $\text{-O-C(CH}_3\text{)(O)-}$ ,  $\text{-S-(CH}_2\text{)}_m\text{-}$ ,  $\text{-C}\equiv\text{C-CH}_2\text{-}$ , or  
 $\text{-C}\equiv\text{C-(CH}_2\text{)}_2\text{-}$

wherein m is an integer 2 or 3;

- 25 R is hydrogen,  $\text{H}_2\text{NC(O)alkyl}$ , alkenylalkyl, methyl, heteroaralkyl,  $(\text{C}_3\text{-C}_7\text{ cycloalkyl})\text{alkyl}$ , or  $\text{C}(\text{O})\text{CH}_3$ ;

30 -E-Y- is selected from  $\text{-O-C(=O)-NH-}$ ,  $\text{-S-C(=O)-NH-}$ ,  $\text{-CH=CH-NH-}$ ,  $\text{-N=CH-NH-}$ ,  
 $\text{-NH-C(=O)-NH-}$ ,  $\text{-N=N-NH-}$ , and  $\text{-NH-C(=O)-C(=O)-NH-}$ ;  
 X is hydrogen; and  
 \* denotes *trans*.

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6. A compound according to Claim 1 selected from:

6-[*trans*-4-(3-Phenylpropylamino)cyclohexyl]-3*H*-benzoxazol-2-one;

6-{*trans*-4-[2-(4-Fluorophenoxy)ethylamino]cyclohexyl}-3*H*-benzoxazol-2-one;

6-[*trans*-4-(2-Phenoxyethylamino)cyclohexyl]-3*H*-benzoxazol-2-one;

6-{*trans*-4-[3-(4-Fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;

6-{*cis*-4-[3-(4-Fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;

6-[*trans*-4-(2-Phenylsulfanylethylamino)cyclohexyl]-3*H*-benzoxazol-2-one;

6-[*cis*-4-(2-Phenylsulfanylethylamino)cyclohexyl]-3*H*-benzoxazol-2-one;

6-[4-(3-Phenylpropylamino)cyclohex-1-enyl]-3*H*-benzoxazol-2-one;

6-{*trans*-4-[2-(4-Fluorophenylsulfanyl)ethylamino]cyclohexyl}-3*H*-benzoxazol-2-one;

6-{*trans*-4-[(*R*)-1-Methyl-3-phenylpropylamino]cyclohexyl}-3*H*-benzoxazol-2-one;

6-{*trans*-4-[(*S*)-1-Methyl-3-phenylpropylamino]cyclohexyl}-3*H*-benzoxazol-2-one;

6-{*trans*-4-[(1*S*,2*S*)-2-Hydroxy-2-(4-methoxyphenyl)-1-methylethylamino]cyclohexyl}-3*H*-benzoxazol-2-one;

6-{*cis*-4-[(1*S*,2*S*)-2-Hydroxy-2-(4-methoxyphenyl)-1-methylethylamino]cyclohexyl}-3*H*-benzoxazol-2-one;

6-{*trans*-4-[(1*S*,2*R*)-2-Hydroxy-1-methyl-2-phenylethylamino]cyclohexyl}-3*H*-benzoxazol-2-one;

6-[*cis*-4-(3-*p*-Tolylpropylamino)cyclohexyl]-3*H*-benzoxazol-2-one;

6-[*trans*-4-(3-*p*-Tolylpropylamino)cyclohexyl]-3*H*-benzoxazol-2-one;

6-[*trans*-4-(2-Benzenesulfinylethylamino)cyclohexyl]-3*H*-benzoxazol-2-one;

6-[*trans*-4-(2-Benzenesulfonylethylamino)cyclohexyl]-3*H*-benzoxazol-2-one;

6-{*trans*-4-[Methyl(3-phenylpropyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one;

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- 6-(*trans*-4-{[3-(4-Fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-  
benzoxazol-2-one;
- 6-(*cis*-4-{[3-(4-Fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-  
benzoxazol-2-one;
- 5 6-{*trans*-[4-(2-Methyl-3-phenylpropylamino)cyclohexyl]}-3*H*-  
benzoxazol-2-one
- 6-{*trans*-4-[Methyl(2-methyl-3-phenylpropyl)amino]cyclohexyl}-3*H*-  
benzoxazol-2-one;
- 6-{*trans*-[4-(3-Phenyl-prop-2-ynylamino)cyclohexyl]}-3*H*-benzoxazol-2-  
10 one;
- 6-{*trans*-4-[Methyl(3-phenylprop-2-ynyl)amino]cyclohexyl}-3*H*-  
benzoxazol-2-one;
- 6-{*trans*-4-[2-(4-Fluorophenylsulfanylethyl)methylamino]cyclohexyl}-  
3*H*-benzoxazol-2-one;
- 15 6-{*trans*-4-[3-(4-Trifluoromethylphenyl)propylamino]cyclohexyl}-3*H*-  
benzoxazol-2-one;
- 6-{*trans*-4-[Methyl-3-(*p*-tolylpropyl)amino]cyclohexyl}-3*H*-benzoxazol-  
2-one;
- 6-{*trans*-4-[Methyl(2-phenoxyethyl)amino]cyclohexyl}-3*H*-benzoxazol-2-  
20 one;
- 6-{*trans*-4-[Methyl-3-(4-trifluoromethylphenyl)propylamino]cyclohexyl}-  
3*H*-benzoxazol-2-one;
- 6-{*trans*-4-[3-(2,4-Difluorophenyl)propylamino]cyclohexyl}-3*H*-  
benzoxazol-2-one;
- 25 6-(*trans*-4-{[3-(2,4-Difluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-  
benzoxazol-2-one;
- 6-(*trans*-4-{[3-(4-Isopropylphenyl)propyl]methylamino}cyclohexyl)-3*H*-  
benzoxazol-2-one;
- 6-(*trans*-4-{[3-(4-Isobutylphenyl)propyl]methylamino}cyclohexyl)-3*H*-  
30 benzoxazol-2-one;
- 6-(*trans*-4-{[Ethyl-[3-(4-fluorophenyl)propyl]amino}cyclohexyl)-3*H*-  
benzoxazol-2-one;

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6-(*trans*-4-{Ethyl-[3-(4-trifluoromethylphenyl)propyl]amino}cyclohexyl)-  
3*H*-benzoxazol-2-one;

6-(*trans*-4-{Ethyl-[(*R*)-1-methyl-3-phenylpropyl]amino}cyclohexyl)-3*H*-  
benzoxazol-2-one;

5 6-(*trans*-4-{Ethyl-[(*S*)-1-methyl-3-phenylpropyl]amino}cyclohexyl)-3*H*-  
benzoxazol-2-one;

6-{*trans*-4-[[3-(4-Fluorophenyl)propyl]-(2-hydroxyethyl)amino]-  
cyclohexyl}-3*H*-benzoxazol-2-one;

10 6-(*trans*-4-{Cyclopropylmethyl-[3-(4-fluorophenyl)propyl]amino}-  
cyclohexyl)-3*H*-benzoxazol-2-one;

6-(*trans*-4-{[3-(4-Fluorophenyl)propyl]furan-3-  
cylmethylamino}cyclohexyl)-3*H*-benzoxazol-2-one;

6-(*trans*-4-{Allyl-[3-(4-Fluorophenyl)propyl]amino}cyclohexyl)-3*H*-  
benzoxazol-2-one;

15 6-(*trans*-4-{[3-(4-Fluorophenyl)propyl]isobutylamino}cyclohexyl)-3*H*-  
benzoxazol-2-one;

6-(*trans*-4-{(2-Aminoethyl)-[3-(4-fluorophenyl)propyl]amino}-  
cyclohexyl)-3*H*-benzoxazol-2-one;

20 2-{[3-(4-Fluorophenyl)propyl]-[4-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-  
cyclohexyl]amino}acetamide;

(*S*)-6-{*trans*-4-[1-(4-Fluorophenylsulfanyl)pentan-2-ylamino]cyclohexyl}-  
3*H*-benzoxazol-2-one;

(*S*)-6-{*trans*-4-[Ethyl(1-(4-fluorophenylsulfanyl)pentan-2-yl)amino]-  
cyclohexyl}-3*H*-benzoxazol-2-one;

25 6-[*trans*-4-(3-Phenylbutylamino)cyclohexyl]-3*H*-benzoxazol-2-one;

6-[*trans*-4-(Methyl-3-phenylbutylamino)cyclohexyl]-3*H*-benzoxazol-2-  
one;

6-{*trans*-4-[3-(4-Chlorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-  
2-one;

30 6-(*trans*-4-{[3-(4-Chlorophenyl)propyl]methylamino}cyclohexyl)-3*H*-  
benzoxazol-2-one;

6-(*trans*-4-{[3-(2,4-Dichlorophenyl)propyl]methylamino}cyclohexyl)-3*H*-  
benzoxazol-2-one;

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6-(*trans*-4-[3-(3,5-Difluorophenyl)propylamino]cyclohexyl)-3*H*-  
benzoxazol-2-one;

6-(*trans*-4-{[3-(3,5-Difluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-  
benzoxazol-2-one;

5 6-(*trans*-4-[3-(3,4-Difluorophenyl)propylamino]cyclohexyl)-3*H*-  
benzoxazol-2-one;

6-(*trans*-4-{[3-(3,4-Difluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-  
benzoxazol-2-one;

10 6-(*trans*-4-{[3-(2,3,4-Trifluorophenyl)propyl]methylamino}cyclohexyl)-  
3*H*-benzoxazol-2-one;

6-(4-{[3-(*trans*-4-Dimethylaminophenyl)propyl]methylamino}-  
cyclohexyl)-3*H*-benzoxazol-2-one;

6-(*trans*-4-{[3-(2,4,6-Trifluorophenyl)propyl]methylamino}cyclohexyl)-  
3*H*-benzoxazol-2-one;

15 6-(*trans*-4-[3-(2,4-Dimethylphenyl)propylamino]cyclohexyl)-3*H*-  
benzoxazol-2-one;

6-(*trans*-{4-[Methyl(2,4-dimethylphenylpropyl)amino]cyclohexyl})-3*H*-  
benzoxazol-2-one;

20 6-{*trans*-4-[3-(2-Chloro-4-fluorophenyl)propylamino]cyclohexyl}-3*H*-  
benzoxazol-2-one;

6-(*trans*-4-{[3-(2-Chloro-4-fluorophenyl)propyl]methylamino}-  
cyclohexyl)-3*H*-benzoxazol-2-one;

6-{*trans*-4-[3-(4-Chloro-2-fluorophenyl)propylamino]cyclohexyl}-3*H*-  
benzoxazol-2-one;

25 6-(*trans*-4-{[3-(4-Chloro-2-fluorophenyl)propyl]methylamino}-  
cyclohexyl)-3*H*-benzoxazol-2-one;

6-(*trans*-4-[3-(4-Fluoro-2-methylphenyl)propylamino]cyclohexyl)-3*H*-  
benzoxazol-2-one;

30 6-(*trans*-{4-[Methyl(4-fluoro-2-methylphenylpropyl)amino]cyclohexyl})-  
3*H*-benzoxazol-2-one;

6-{*trans*-4-[3-(3-Fluoro-2-methylphenyl)propylamino]cyclohexyl}-3*H*-  
benzoxazol-2-one;



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6-(*trans*-4-{[3-(3-Fluoro-2-methylphenyl)propyl]methylamino}-  
cyclohexyl)-3*H*-benzoxazol-2-one;

6-{*trans*-4-[3-(2-Fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-  
2-one;

5 6-(*trans*-4-{[3-(2-Fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-  
benzoxazol-2-one;

6-{*trans*-4-[3-(3-Fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-  
2-one;

10 6-(*trans*-4-{[3-(3-Fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-  
benzoxazol-2-one;

6-{*trans*-4-[(3-Cyclohexylpropyl)amino]cyclohexyl}-3*H*-benzoxazol-2-  
one;

6-{*trans*-4-[(3-Cyclohexylpropyl)methylamino]cyclohexyl}-3*H*-  
benzoxazol-2-one;

15 6-{*trans*-4-[4-(3-Thiophen-3-yl)propylamino]cyclohexyl}-3*H*-benzoxazol-  
2-one;

6-[*trans*-4-{[3-(3-Thiophen-3-yl)propyl]methylamino}cyclohexyl]-3*H*-  
benzoxazol-2-one;

20 6-{*trans*-4-[Methyl(3-thiazol-2-ylpropyl)amino]cyclohexyl}-3*H*-  
benzoxazol-2-one;

6-(*trans*-4-{Methyl-[2-(methylphenylamino)ethyl]amino}cyclohexyl)-3*H*-  
benzoxazol-2-one;

N-(2-{Methyl-[4-(2-oxo-2,3-dihydrobenzoxazol-6-yl)cyclohexyl]amino}-  
ethyl)benzamide;

25 N-{2-[4-(2-Oxo-2,3-dihydrobenzoxazol-6-yl)cyclohexylamino]ethyl}-  
benzamide;

6-{*trans*-4-[3-(4-Fluorophenyl)propylamino]cyclohexyl}-3*H*-benzthiazol-  
2-one;

30 3-(4-Fluorophenyl)-N-methyl-N-[*trans*-4-(2-oxo-2,3-dihydrobenzoxazol-  
6-yl)cyclohexyl]propionamide;

6-(*trans*-4-{[3-(4-Fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-  
benzthiazol-2-one;

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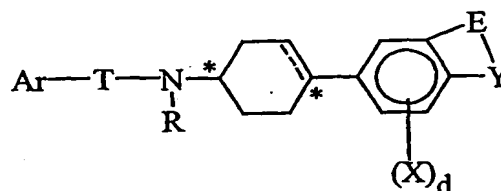
5-{*trans*-4-[3-(4-Fluorophenyl)propylamino]cyclohexyl}-1,3-dihydrobenzoimidazol-2-one;

5-{*trans*-4-{[3-(4-Fluorophenyl)propyl]methylamino}cyclohexyl}-1,3-dihydrobenzoimidazol-2-one;

5 6-(4-{[3-(4-Fluorophenyl)propyl]methyl-amino}cyclohexyl)-5-methyl-3*H*-benzoxazol-2-one; and

6-(*trans*-4-{[3-(4-Fluorophenyl)propyl]methylamino}cyclohexyl)-5-methoxy-3*H*-benzoxazol-2-one.

7. A compound of Formula II



II

or a pharmaceutically acceptable salt thereof wherein:

Ar is substituted 1 to 3 times or unsubstituted aryl or substituted 1 to

3 times or unsubstituted heteroaryl, which heteroaryl is from 5 to

14 atoms having from 1 to 2 heteroatoms selected from N, O, and S

wherein the substituents are selected from the groups F, Cl, Br, I,

OH, NH<sub>2</sub>, SH, CN, NO<sub>2</sub>, OCH<sub>3</sub>, OC(O)CH<sub>3</sub>, CF<sub>3</sub>,

OCH<sub>2</sub>CH<sub>2</sub>OH, NHC(O)CH<sub>3</sub>, NHCH<sub>3</sub>, or N(CH<sub>3</sub>)<sub>2</sub>;

-E-Y- is selected from the group consisting of -CH=CH-N(H)-,

-(CH<sub>2</sub>)<sub>2</sub>-N(H)-,

-CH=N-N(H)-,

-C(O)-CH<sub>2</sub>-N(H)-,

-CH<sub>2</sub>-C(O)-N(H)-,

-CH<sub>2</sub>-S(O)-N(H)-,

-CH<sub>2</sub>-S(O)<sub>2</sub>-N(H)-,

-CH=CH-CH(OH)-,

-(CH<sub>2</sub>)<sub>2</sub>-CH(OH)-,

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-C(O)-CH<sub>2</sub>-C(O)-,

-C(O)-NH-C(O)-,

-N=CH-N(H)-,

-N(H)-C(O)-N(H)-,

5

-O-C(O)-NH-,

-S-C(O)-NH-,

-O-N=CH(OH)-,

-S-N=CH(OH)-,

-N=N-N(H)-,

10

-CH=CH-CH=C(OH)-,

-(CH<sub>2</sub>)<sub>3</sub>-CH(OH)-,-(CH<sub>2</sub>)<sub>2</sub>-S(O)-N(H)-,-(CH<sub>2</sub>)<sub>2</sub>-S(O)<sub>2</sub>-N(H)-,

-CH=CH-C(O)-N(H)-,

15

-C(O)-NH-N=C(OH)-,

-CH=N-NH-C(O)-,

-CH=N(O)-N=C(OH)-,

-N(H)-C(O)-N(H)-C(O)-,

-N=CH-C(O)-NH-,

20

-O-CH<sub>2</sub>-C(O)-NH-,-S-CH<sub>2</sub>-C(O)-NH-, or

-N(H)-C(O)-C(O)-N(H)-,

25

$$T \text{ is } (A)_{0-1}-N-(U)_{0-1}-(C)_t \text{ or } (A)_{0-1}-N-(C)_t-(U)_{0-1},$$

$\begin{array}{c} R_3 \\ | \\ (A)_{0-1} \end{array}$

$\begin{array}{c} R_1 \\ | \\ (U)_{0-1} \end{array}$

$\begin{array}{c} R_3 \quad R_1 \\ | \quad | \\ (C)_t \end{array}$

$\begin{array}{c} R_2 \\ | \\ (U)_{0-1} \end{array}$

30

$$\text{wherein } U \text{ is } -\text{CH}_2-, -\text{C}-, -\text{S}(\text{O})-, \text{ or } -\text{S}(\text{O})_2-,$$

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O  
||

A is -CH<sub>2</sub>-, -C-, -S(O)-, or -S(O)<sub>2</sub>-,

t is an integer from 1 to 3,

5

R<sub>1</sub> and R<sub>2</sub> are independently selected from hydrogen, alkyl, OH,

hydroxyalkyl, aminoalkyl, thioalkyl, aryl, aralkyl, heteroaryl,  
heteroaralkyl, guanidiny, (aminocarbonyl)alkyl-, carboxyalkyl-,  
(methylthio)-alkyl-, or N(R<sub>4</sub>)(R<sub>5</sub>) wherein R<sub>4</sub> and R<sub>5</sub> are  
independently selected from hydrogen, alkyl, aralkyl, heteroaryl,  
heteroaralkyl, ureidoalkyl, aminoalkyl, hydroxyalkyl, or thioalkyl,

10

R<sub>3</sub> is hydrogen, alkyl, OH, or aralkyl,

R is hydrogen, alkyl, C(O)R<sub>6</sub>, C(O)OR<sub>6</sub>, C(O)NHR<sub>6</sub>, alkyl -CO<sub>2</sub>NH<sub>2</sub>,

aralkyl, hydroxyalkyl, (C<sub>3</sub>-C<sub>7</sub> cycloalkyl) alkyl, aminoalkyl,  
amino(hydroxy)alkyl, carboxyalkyl, heteroaralkyl, alkenyl-alkyl, or  
OH wherein R<sub>6</sub> is alkyl or aralkyl;

15

X is independently selected from hydrogen or an electron withdrawing  
group;

-- denotes a single or a double bond; and

\* denotes *cis* or *trans* or a mixture thereof.

20

8. A compound according to Claim 7 wherein:

X is independently selected from hydrogen or an electron withdrawing  
group selected from the group consisting of halogen, nitro, cyano,  
aminoalkyl, CF<sub>3</sub>, C(O)CH<sub>3</sub>, and haloalkyl.

9. A compound according to Claim 7 wherein:

25

Ar is unsubstituted or substituted phenyl;

X is independently selected from hydrogen or an electron withdrawing  
group selected from the group consisting of halogen, nitro, cyano,  
aminoalkyl, CF<sub>3</sub>, C(O)CH<sub>3</sub>, and haloalkyl;

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-E-Y- is selected from  $\begin{array}{c} \text{O} \\ \parallel \\ -\text{O}-\text{C}-\text{NH}- \end{array}$ ,  $\begin{array}{c} \text{O} \\ \parallel \\ -\text{S}-\text{C}-\text{NH}- \end{array}$ ,  $-\text{CH}=\text{CH}-\text{NH}-$ ,  $-\text{N}=\text{CH}-\text{NH}-$ ,

5

$\begin{array}{c} \text{O} \\ \parallel \\ -\text{NH}-\text{C}-\text{NH}- \end{array}$ ,  $-\text{N}=\text{N}-\text{NH}-$ , and  $\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ -\text{NH}-\text{C}-\text{C}-\text{NH}- \end{array}$ ; and

\* denotes *trans*.

10. A compound according to Claim 7 wherein:

Ar is unsubstituted or substituted phenyl;

10

Ar and the nitrogen atom bearing R are separated by 3 or 4 atoms;

X is independently selected from hydrogen or an electron withdrawing group selected from the group consisting of halogen, nitro, cyano, aminoalkyl,  $\text{CF}_3$ ,  $\text{C}(\text{O})\text{CH}_3$ , and haloalkyl.

15

-E-Y- is selected from  $\begin{array}{c} \text{O} \\ \parallel \\ -\text{O}-\text{C}-\text{NH}- \end{array}$ ,  $\begin{array}{c} \text{O} \\ \parallel \\ -\text{S}-\text{C}-\text{NH}- \end{array}$ ,  $-\text{CH}=\text{CH}-\text{NH}-$ ,  $-\text{N}=\text{CH}-\text{NH}-$ ,

$\begin{array}{c} \text{O} \\ \parallel \\ -\text{NH}-\text{C}-\text{NH}- \end{array}$ ,  $-\text{N}=\text{N}-\text{NH}-$ , and  $\begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ -\text{NH}-\text{C}-\text{C}-\text{NH}- \end{array}$ ; and

20

\* denotes *trans*.

11. A compound according to Claim 7 wherein:

Ar is unsubstituted or substituted phenyl;

T is

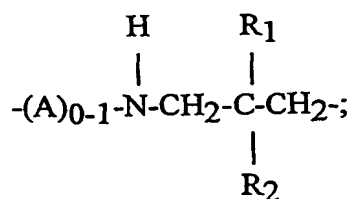
25

$\begin{array}{c} \text{H} \text{ R}_1 \text{ O} \\ | \quad | \quad \parallel \\ (\text{A})_{0-1}-\text{N}-\text{C}-\text{C}- \\ | \\ \text{R}_2 \end{array}$ ,  $\begin{array}{c} \text{H} \quad \text{R}_1 \text{ O} \\ | \quad | \quad \parallel \\ (\text{A})_{0-1}-\text{N}-\text{CH}_2-\text{C}-\text{C}- \\ | \\ \text{R}_2 \end{array}$ ,  $\begin{array}{c} \text{H} \text{ O} \text{ R}_1 \\ | \quad \parallel \quad | \\ (\text{A})_{0-1}-\text{N}-\text{C}-\text{C}- \\ | \\ \text{R}_2 \end{array}$ ,  $\begin{array}{c} \text{H} \text{ O} \text{ R}_1 \\ | \quad \parallel \quad | \\ (\text{A})_{0-1}-\text{N}-\text{C}-\text{C}-\text{CH}_2- \\ | \\ \text{R}_2 \end{array}$ ,

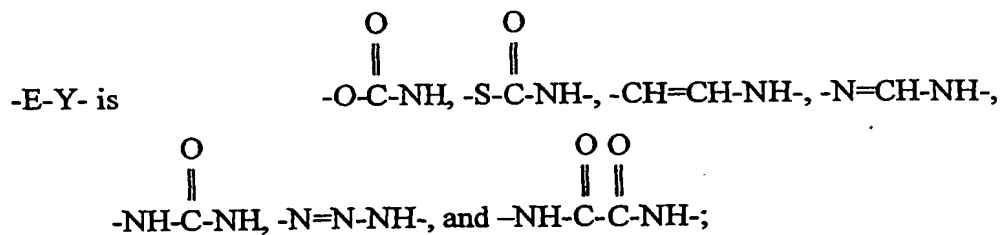
30

$\begin{array}{c} \text{H} \text{ R}_1 \\ | \quad | \\ -(\text{A})_{0-1}-\text{N}-\text{C}-\text{CH}_2- \\ | \\ \text{R}_2 \end{array}$ ,  $\begin{array}{c} \text{H} \quad \text{R}_1 \\ | \quad | \\ (\text{A})_{0-1}-\text{N}-\text{CH}_2-\text{C}-\text{CH}_2- \\ | \\ \text{R}_2 \end{array}$ ,  $\begin{array}{c} \text{H} \quad \text{R}_1 \\ | \quad | \\ (\text{A})_{0-1}-\text{N}-\text{CH}_2-\text{C}- \\ | \\ \text{R}_2 \end{array}$ ; or

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R is hydrogen, alkenylalkyl,  $\text{H}_2\text{NC(O)alkyl}$ , methyl, heteroaralkyl, ( $\text{C}_3\text{-C}_7$  cycloalkyl)alkyl, or  $\text{C(O)CH}_3$ ;



X is hydrogen; and

\* denotes *trans*.

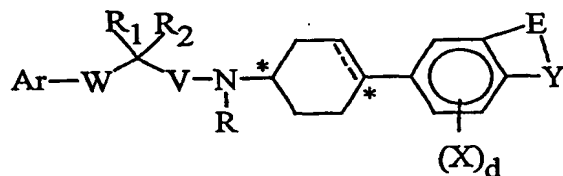
12. A compound according to Claim 7 selected from:

6-[*trans*-4-(2-Phenylaminoethylamino)cyclohexyl]-3*H*-benzoxazol-2-one;

and

N-(2-{Methyl-[4-(2-oxo-2,3-dihydrobenzoxazol-6-yl)cyclohexyl]amino}-ethyl)benzamide.

13. A compound of Formula III



III

or a pharmaceutically acceptable salt thereof wherein:

Ar is substituted 1 to 3 times or unsubstituted aryl or substituted 1 to

3 times or unsubstituted heteroaryl, which heteroaryl is from 5 to

14 atoms having from 1 to 2 heteroatoms selected from N, O, and S

wherein the substituents are selected from the groups F, Cl, Br, I,

OH,  $\text{NH}_2$ , SH, CN,  $\text{NO}_2$ ,  $\text{OCH}_3$ ,  $\text{OC(O)CH}_3$ ,  $\text{CF}_3$ ,

$\text{OCH}_2\text{CH}_2\text{OH}$ ,  $\text{NHC(O)CH}_3$ ,  $\text{NHCH}_3$ , or  $\text{N(CH}_3)_2$ ;

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-E-Y- is selected from the group consisting of -CH=CH-N(H)-,

- (CH<sub>2</sub>)<sub>2</sub>-N(H)-,

-CH=N-N(H)-,

-C(O)-CH<sub>2</sub>-N(H)-,

5 -CH<sub>2</sub>-C(O)-N(H)-,

-CH<sub>2</sub>-S(O)-N(H)-,

-CH<sub>2</sub>-S(O)<sub>2</sub>-N(H)-,

-CH=CH-CH(OH)-,

10 -(CH<sub>2</sub>)<sub>2</sub>-CH(OH)-,

-C(O)-CH<sub>2</sub>-C(O)-,

-C(O)-NH-C(O)-,

-N=CH-N(H)-,

-N(H)-C(O)-N(H)-,

-O-C(O)-NH-,

15 -S-C(O)-NH-,

-O-N=CH(OH)-,

-S-N=CH(OH)-,

-N=N-N(H)-,

-CH=CH-CH=C(OH)-,

20 -(CH<sub>2</sub>)<sub>3</sub>-CH(OH)-,

-(CH<sub>2</sub>)<sub>2</sub>-S(O)-N(H)-,

-(CH<sub>2</sub>)<sub>2</sub>-S(O)<sub>2</sub>-N(H)-,

-CH=CH-C(O)-N(H)-,

-C(O)-NH-N=C(OH)-,

25 -CH=N-NH-C(O)-,

-CH=N(O)-N=C(OH)-,

-N(H)-C(O)-N(H)-C(O)-,

-N=CH-C(O)-NH-,

-O-CH<sub>2</sub>-C(O)-NH-,

30 -S-CH<sub>2</sub>-C(O)-NH-, or

-N(H)-C(O)-C(O)-N(H)-;

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$$\begin{array}{c} \text{O} \\ || \\ \text{---} \end{array}$$

V is  $-(\text{CH}_2)_n-$ ,  $-\text{C}-$ ,  $-\text{S}(\text{O})-$ , or  $-\text{S}(\text{O})_2-$ ;

$$\begin{array}{c} \text{O} \\ || \\ \text{---} \end{array}$$

W is  $-(\text{CH}_2)_n-$ ,  $-\text{C}-$ ,  $-\text{S}(\text{O})-$ ,  $-\text{S}(\text{O})_2-$ ,  $-\text{O}-$ ,  $-\text{S}-$ ,  $-\text{C}\equiv\text{C}-$ , or *entgegen* or *zusammen*  $-\text{CH}(\text{R}_1)=\text{CH}(\text{R}_2)-$ ;

d is an integer from 0 to 2;

n is an integer from 1 to 6;

q is an integer from 0 to 6;

$\text{R}_1$  and  $\text{R}_2$  are independently selected from the group consisting of

hydrogen, alkyl, OH, hydroxyalkyl, aminoalkyl, aralkyl, or  $\text{N}(\text{R}_4)(\text{R}_5)$  wherein  $\text{R}_4$  and  $\text{R}_5$  are independently selected from hydrogen, alkyl, aralkyl, heteroaryl, heteroaralkyl, aminoalkyl, hydroxyalkyl, and thioalkyl;

R is hydrogen, alkyl,  $\text{C}(\text{O})\text{R}_6$ ,  $\text{C}(\text{O})\text{OR}_6$ ,  $\text{C}(\text{O})\text{NHR}_6$ ,  $-\text{alkyl}-\text{C}(\text{O})\text{NH}_2$ , aralkyl,  $(\text{C}_3\text{-C}_7\text{ cycloalkyl})\text{-alkyl}$ , aminoalkyl, amino(hydroxy)alkyl, carboxyalkyl, heteroaralkyl, alkenylalkyl, or OH wherein  $\text{R}_6$  is alkyl or aralkyl;

X is independently selected from hydrogen or an electron withdrawing group;

-- denotes a single or a double bond; and

\* denotes *cis* or *trans* or a mixture thereof.

14. A compound according to Claim 3 wherein:

Ar is unsubstituted or substituted phenyl;

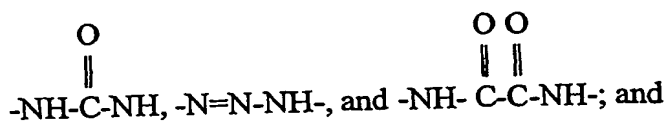
X is independently selected from hydrogen or an electron withdrawing group selected from the group consisting of halogen, nitro, cyano, aminoalkyl,  $\text{CF}_3$ ,  $\text{C}(\text{O})\text{CH}_3$ , and haloalkyl;

$$\begin{array}{cc} \text{O} & \text{O} \\ || & || \\ \text{---} & \text{---} \end{array}$$

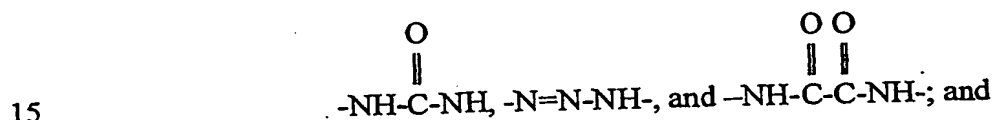
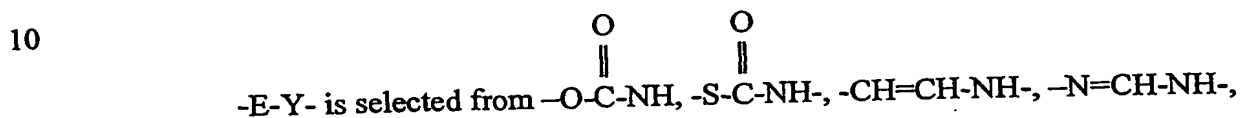
-E-Y- is selected from  $-\text{O}-\text{C}-\text{NH}-$ ,  $-\text{S}-\text{C}-\text{NH}-$ ,  $-\text{CH}=\text{CH}-\text{NH}-$ ,  $-\text{N}=\text{CH}-\text{NH}-$ ,



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\* denotes *cis*.

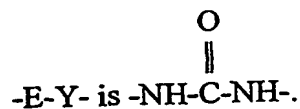
- 5 15. A compound according to Claim 3 wherein:  
 Ar is unsubstituted or substituted phenyl;  
 X is independently selected from hydrogen or an electron withdrawing  
 group selected from the group consisting of halogen, nitro, cyano,  
 aminoalkyl, CF<sub>3</sub>, C(O)CH<sub>3</sub>, and haloalkyl;

\* denotes *trans*.

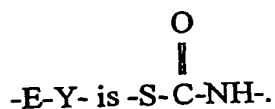
16. The compound of Claim 1, 7, or 3 wherein:



17. The compound of Claim 1, 7, or 3 wherein:



- 25 18. The compound of Claim 1, 7, or 3 wherein:



- 30 19. A pharmaceutical composition useful for treating disorders responsive to  
 the selective blockade of N-methyl-D-aspartate receptor subtypes,  
 optionally disorders as stroke, cerebral ischemia, trauma, hypoglycemia,  
 neurodegenerative disorders, anxiety, depression, migraine headache,

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convulsions, aminoglycoside antibiotics-induced hearing loss, psychosis, glaucoma, CMV retinitis, opioid tolerance or withdrawal, chronic pain, or urinary incontinence the compositions comprising a pharmaceutically acceptable carrier or diluent and a therapeutically effective amount of at least one compound of Claim 1, Claim 7, or Claim 3.

- 5
20. A pharmaceutical composition according to Claim 19, wherein the neurodegenerative disorder is Parkinson's disease.
21. A pharmaceutical composition according to Claim 19, further comprising a dopamine agonist or precursor thereof in amount effective to treat Parkinson's disease.
- 10
22. A method for treating disorders responsive to the selective blockade of N-methyl-D-aspartate receptor subtypes in a mammal suffering thereof which comprises administering in unit dosage form at least one compound represented by Formula I of Claim 1 or Formula II of Claim 7 or Formula III of Claim 3.
- 15
23. A method according to Claim 22, wherein the disorder is Parkinson's disease.
24. A method according to Claim 22, further comprising administering in unit dosage form a compound any one of Formula I-III to a mammal suffering from Parkinson's disease.
- 20

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 01/14763

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 C07D263/58 C07D277/68 C07D235/26 C07D413/12 C07D417/12  
A61K31/423 A61K31/428 A61K31/4184 A61P25/16

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 C07D C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 982 026 A (F. HOFFMANN-LA ROCHE AG) 1 March 2000 (2000-03-01) the whole document	1-24
A	WO 99 48891 A (MERCK PATENT GMBH) 30 September 1999 (1999-09-30) the whole document	1,7,13, 19,22
A	DE 44 38 055 A (DR. KARL THOMAE GMBH) 2 May 1996 (1996-05-02) page 10, line 20, and page 15, line 6	1,7,13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
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- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

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- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \*G\* document member of the same patent family

Date of the actual completion of the international search

7 September 2001

Date of mailing of the international search report

13/09/2001

Name and mailing address of the ISA

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Information on patent family members

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